SIMPONI™ (golimumab) Formulary Dossier

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LIST OF APPENDICES

The following assessments were used in clinical studies to evaluate clinical efficacy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

ABBREVIATIONS AND DEFINITIONS OF TERMS

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AAD	American Academy of Dermatology
ACR	American College of Rheumatology
ACR 20	20% improvement in the counts of the numbers of tender and swollen joints and ≥3 items from the following: physician overall disease activity, patient overall disease activity, patient evaluation of pain, a score of physical disability, and improvements in blood acute-phase reactants
ACR 50	A 50% improvement in the parameters described for ACR 20
ACR 70	A 70% improvement in the parameters described for ACR 70
ACR-N	ACR-N index of improvement
AS	ankylosing spondylitis
ASAS	ASsessment in AS International Working Group criteria
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Function Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BSA	body surface area
CRP	C-reactive protein
DAS28	Disease Activity Score in 28 joints
DMARD(s)	disease-modifying antirheumatic drug(s)
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GO-AFTER	Golimumab After Former Anti-TNF Therapy Evaluated in RA
GO- BEFORE	Golimumab Before Employing Methotrexate as the First-line Option in the Treatment of Rheumatoid Arthritis of Early Onset
GO-FORWARD	Golimumab For Subjects With Active RA Despite MTX
GO-RAISE	Golimumab – A Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF mAB Injection (SC) Given Every Four Weeks
GO-REVEAL	Golimumab – A Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Fully Human Anti-TNF Monoclonal Antibody
HAQ/HAQ-DI	Health Assessment Questionnaire
HCQ	hydroxychloroquine
IgG1κ	immunoglobulin 1- kappa
IQR	interquartile range
IV	intravenous
JSEQ	Jenkins Sleep Evaluation Questionnaire
MCO	Managed Care Organization
MCS	Mental Component Summary score
MTX	methotrexate
NA	not applicable
Nail PGA	Nail Physician Global Assessment
NAPSI	Nail Psoriasis Severity Index
NIH	National Institutes of Health
NNT	number needed to treat
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
PASI	Psoriasis Area and Severity Index
PASI 75	Subjects with ≥ 75% improvement in PASI score from baseline
PASI 90	Subjects with ≥ 90% improvement in PASI score from baseline
PASI 50	Subjects with ≥ 50% improvement in PASI score from baseline
PCS	Physical Component Summary score
PGA	Physician's Global Assessment (of disease severity)
PMPM	per member per month
PsA	psoriatic arthritis

PTMPM	per treated member per month
PUVA	psoralen plus ultraviolet A light
QoL (HR-QoL)	quality of life
RA	rheumatoid arthritis
SC	subcutaneous/subcutaneously
SD	standard deviation
SF-36	Short-Form 36
SSZ	sulfasalazine
$t_{1/2}$	half-life
t_{max}	median time to reach the maximum serum concentration
TB	tuberculosis
TNF (TNF-α)	tumor necrosis factor
US	United States
VAS	Visual Analogue Scale (Score)
Vd	median volume of distribution during the terminal phase
WAC	Wholesale Acquisition Cost

EXECUTIVE SUMMARY

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OVERVIEW

- SIMPONI is a human IgG1κ monoclonal antibody specific for human tumor necrosis factor-α (TNF-α) that binds to both the soluble and transmembrane bioactive forms of human TNF-α. This interaction prevents the binding of TNF-α to its receptors, thereby inhibiting the biological activity of TNF-α (a cytokine protein). Elevated TNF-α levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as RA, PsA, and AS. TNF-α is an important mediator of the articular inflammation that is characteristic of these diseases.
- SIMPONI is the first anti-TNF agent administered SC and dosed once a month for the treatment of RA, PsA and AS.
- SIMPONI satisfies an unmet need for patients with rheumatic disease (RA, AS, and PsA) as current treatment options in rheumatology may not be suitable for all patients.

FDA APPROVED INDICATIONS

- SIMPONI is a TNF blocker indicated for the treatment of adult patients with:
    - Moderately to severely active RA, in combination with MTX.
    - Active PsA, alone or in combination with MTX.
    - Active AS.

CLINICAL FEATURES OF SIMPONI

The efficacy and safety of SIMPONI were evaluated in 5 multicenter, randomized, double-blind, controlled trials including 2303 patients ≥18 years of age with moderately to severely active RA, active PsA, and active AS. SIMPONI was administered subcutaneously every 4 weeks. Double-blind controlled efficacy data were collected and analyzed through Week 24. Following is a summary of baseline demographics and disease characteristics.

Table 1. Summary of demographics and other baseline disease characteristics at baseline

	GO-BEFORE	GO-FORWARD	GO-AFTER	GO-REVEAL	GO-RAISE
Female, %	82.9	80.6	80.0	39.8	28.4
Age, years*	50.0	51.0	54.0	47.0	38.5
Disease duration, years*	1.0 – 1.8	4.5 – 6.7	8.65 – 9.80	5.0 – 5.5	5.15 – 7.25
SJC*	11.0 – 14.0	11.0 – 13.0	13.0 – 14.0	9.5 – 11.0	-
TJC*	24.5 – 26.0	21.0 – 26.0	26.0 – 27.0	18.0 – 19.0	-
CRP level, mg/dL*	1.3 – 1.4	0.80 – 1.0	0.75 – 1.0	0.6	0.9 – 1.15
HAQ scores*	1.50 – 1.75	1.25 – 1.38	1.50 – 1.75	1.0 – 1.13	4.93 – 5.38§
1-2 previous DMARDs, %	50.2†	61.5	39.2 – 52.3	66.4 – 74.7	50.0 – 52.6
Concomitant MTX, mg/week*	20.0‡	15.0	15.0 – 17.5	15.0	12.5 – 15.0
Concomitant NSAIDs, %	83.6 – 86.8	82.7 – 86.5	59.4 – 61.8	75.3 – 77.9	87.9 – 92.3
Concomitant corticosteroids, %	50.3 – 54.8	65.4 – 75.3	44.7 – 60.5	13.0 – 18.5	12.9 – 18.8

*Median; †DMARDs other than MTX; ‡MTX was administered orally at a dose of 10 mg/week starting at week 0, with a dose escalation to 20 mg/week by week 8; the 20 mg/week dose was to be continued through Week 52; §BASFI (0 – 10)

Rheumatoid Arthritis

The FDA approval of SIMPONI, in combination with MTX, as maintenance therapy for the treatment of moderately to severely active RA was based on data from three phase III trials (GO-AFTER, GO-FORWARD and GO-BEFORE) in 1542 patients. Patients were diagnosed according to the American College of Rheumatology (ACR) criteria for ≥3 months prior to administration of study agent. Patients were required to have at least 4 swollen and 4 tender joints. SIMPONI was administered SC at doses of 50 mg or 100 mg every 4 weeks. Patients were allowed to continue stable doses of concomitant low dose

corticosteroids (equivalent to ≤10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials (Keystone EC et al, 2008; Smolen J et al, 2008; Emery P et al, 2008; SIMPONI prescribing information).

- The **GO-BEFORE** trial (n=637) evaluated the use of SIMPONI in patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomized to receive MTX alone (n=160), SIMPONI 50 mg + MTX (n=159), and SIMPONI 100 mg + MTX (n=159), or SIMPONI 100 mg monotherapy (n=159). For patients receiving MTX, MTX was administered at a dose of 10 mg/week beginning at week 0 and increased to 20 mg/week by week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving an ACR 50 response at week 24.
    - At week 24, an ACR 50 response was achieved by 38.4% of patients in the combined SIMPONI + MTX group, compared to 29.4% of patients in the placebo + MTX group. An ACR 50 response was achieved by 40.3% and 29.4% of patients in the SIMPONI 50 mg + MTX group and the placebo + MTX group, respectively (p=0.042).
    - There was no clear evidence of improved ACR score with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). Further, the SIMPONI monotherapy group was not statistically different from the MTX monotherapy group in ACR response.

- The **GO-FORWARD** trial (n=444) evaluated patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomized to receive placebo + MTX (n=133), SIMPONI 50 mg + MTX (n=89), SIMPONI 100 mg + MTX (n=89), or SIMPONI 100 mg monotherapy + placebo (n=133). The primary endpoint was the percentage of patients achieving an ACR 20 response at week 14.
    - The proportion of patients achieving an ACR 20 response at week 14 was significantly greater in the SIMPONI 50 mg + MTX group (55%) versus MTX alone (33%; p≤0.001). Responses were sustained with 60% versus 28% (p≤0.001) of patients, respectively, achieving an ACR 20 response at week 24.
    - There was no clear evidence of improved ACR score with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). Further, the SIMPONI monotherapy group was not statistically different from the MTX monotherapy group in ACR response.
    - ACR 20 responses were observed in 38% of patients in the SIMPONI 50 mg + MTX group at the first assessment (Week 4) after the initial SIMPONI administration.
    - All individual components of the ACR response criteria were significantly improved in the SIMPONI 50mg-treated patients versus MTX alone patients at week 14.
    - A significantly greater improvement in physical function response (change in mean HAQ from baseline to Week 24) was observed with SIMPONI 50 mg, compared to MTX alone: 0.47 vs. 0.13.

- The **GO-AFTER** trial (n=461) was the only pivotal trial to evaluate the use of an anti-TNF agent (SIMPONI) in patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomized to receive placebo (n=155), SIMPONI 50 mg (n=153), and SIMPONI 100 mg (n=153). Patients were allowed to continue concomitant DMARD therapy with MTX, SSZ, and/or HCQ during the study. Discontinuation of prior anti-TNF therapies could have been for reasons including lack of efficacy (58%), intolerance (17%), and/or reasons other than safety or efficacy (40%). The primary endpoint was the percentage of patients achieving an ACR 20 response at week 14.
    - SIMPONI 50 mg (all patients) was significantly better than placebo in improving signs and symptoms of RA, according to ACR 20 (35.3% vs. 18.1%, respectively; p<0.001). There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).
    - In a subset of patients who received SIMPONI 50mg + MTX, the proportion of patients achieving ACR 20, 50 and 70 responses at week 14 were 40%, 18%, and 13%, respectively, compared with placebo + MTX (17%, 6%, and 2%, respectively).
    - ACR 20 responders at week 14 among patients who discontinued previous anti-TNF therapy due to lack of efficacy included 35.7% and 42.7% of patients in the SIMPONI 50 mg and 100 mg

groups, respectively, compared with 17.7% of patients in the placebo group (p=0.006, SIMPONI 50 mg vs. placebo; p<0.001, SIMPONI 100 mg vs. placebo).
- A significantly greater improvement in physical function response (change in mean HAQ from baseline to Week 24) was observed with SIMPONI 50 mg, compared to placebo: 0.25 vs. 0.05.

Psoriatic Arthritis

The FDA approval of SIMPONI, with or without concomitant MTX, as maintenance therapy for the treatment of active disease in patients refractory to NSAID or DMARD therapy was based on data from the phase III trial GO-REVEAL. Patients enrolled in this study (n=405) had PsA diagnosed for at least 6 months. Patients had at least 3 swollen and 3 tender joints and a qualifying psoriatic skin lesion of at least 2 cm in diameter. Patients in the GO-REVEAL study had not been previously treated with an anti-TNF agent. Patients were randomly assigned to placebo (n=113), SIMPONI 50 mg (n=146), or SIMPONI 100 mg (n=146) given SC every 4 weeks. The primary endpoint was an ACR 20 response at week 14. Placebo-controlled efficacy data were collected and analyzed through week 24; blinded active treatment continued through week 52 (Kavanaugh A et al, 2008; Kavanaugh A et al, 2009; SIMPONI prescribing information).

- The **GO-REVEAL** trial demonstrated that SIMPONI 50 mg, with and without MTX, was superior to placebo in reducing joint and skin symptoms in adult patients with active PsA.
  - SIMPONI 50 mg ± MTX, compared with placebo ± MTX, resulted in a significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ACR 20 response at week 14 (51% vs. 9%; p<0.001). There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).
  - Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes.
  - ACR responses observed in the SIMPONI treated groups were similar in patients receiving and not receiving concomitant MTX.
  - ACR 20 responses were observed in 31% of patients in the SIMPONI 50 mg + MTX group at the first assessment (week 4) after the initial SIMPONI administration.
  - Among the 74% of patients in whom at least 3% of the BSA was affected by psoriasis at baseline, 40% of those in the SIMPONI 50 mg group and 58% of those in the SIMPONI 100 mg group achieved a PASI75 response at week 14, compared with 3% of placebo-treated patients (p<0.001 for both doses).
  - SIMPONI 50 mg demonstrated a greater improvement compared to placebo in the change in mean HAQ score from baseline to week 24 (0.33 vs. 0.01, respectively).

Ankylosing Spondylitis

The FDA approval of SIMPONI as maintenance therapy for the treatment of active disease in patients refractory to current or previous NSAID or DMARD therapy was based on data from the phase III trial GO-RAISE. Patients enrolled in this study (n=356) had active AS defined as a BASDAI ≥4 and total back pain score of ≥4 (VAS 0 to 10). Patients were excluded if they were previously treated with an anti-TNF agent or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (n=78), SIMPONI 50 mg (n=138), or SIMPONI 100 mg (n=140) administered SC every 4 weeks (Inman RD et al, 2008; SIMPONI prescribing information).

- The **GO-RAISE** trial demonstrated that SIMPONI 50 mg was superior to placebo in reducing signs and symptoms in adult patients with active AS.
  - SIMPONI ± DMARDs, compared with placebo ± DMARDs resulted in a significant improvement in signs and symptoms as demonstrated by ASAS 20 responses at week 14 (59% vs. 22%; p≤0.001). There was no clear evidence of improved ASAS response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).
  - All individual components of the ASAS response criteria were significantly improved in the SIMPONI 50 mg group vs. the placebo group at week 14.
  - ASAS 20 responses were observed in 48% of patients in the SIMPONI 50 mg + MTX group at the first assessment (week 4) after the initial SIMPONI administration.

DOSING AND ADMINISTRATION

For the treatment of RA, PsA and AS, the SIMPONI dose regiment is 50 mg administered by subcutaneous injection once a month. SIMPONI is available as a single-dose autoinjector containing 50 mg of SIMPONI per 0.5 mL, and a single-dose prefilled syringe containing 50 mg of SIMPONI per 0.5 mL.

For patients with RA, SIMPONI should be given in combination with MTX and for patients with PsA or AS, SIMPONI may be given with or without MTX or other non-biologic DMARDs. For patients with RA, PsA or AS, corticosteroids, non-biologic DMARDs, and/or NSAIDs may be continued during treatment with SIMPONI.

SIMPONI is intended for use under the guidance and supervision of a physician. After proper training in SC injection technique, a patient may self inject with SIMPONI if a physician determines that it is appropriate. Patients should be instructed to follow the directions provided in the Medication Guide for SIMPONI.

Please see accompanying Full Prescribing Information and Medication Guide for SIMPONI.

1. PRODUCT INFORMATION

1.1 PRODUCT DESCRIPTION

A. Generic, Brand Name, and Therapeutic Class

Generic
Golimumab

Brand
SIMPONI™

Therapeutic Class
As a TNF antagonist, SIMPONI is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to both the soluble and transmembrane forms of human TNF-α.

B. Dosage Form
SIMPONI is packaged in a single-dose outer carton. SIMPONI is available in packs of 1 prefilled syringe (50 mg/0.5 mL) or 1 SmartJect™ autoinjector (50 mg/0.5 mL).

C. National Drug Code
The NDC number for the prefilled syringe is 57894-070-01. The NDC number for the SmartJect™ autoinjector is 57894-070-02.

D. **Product Labeling** (enclosed)

E. Pricing (Please see account representative)

F. DPA/AHFS Drug Classification
Disease-modifying antirheumatic drug (DMARD)

G. Indications

FDA-Approved Indications

- SIMPONI is a TNF blocker indicated for the treatment of adult patients with:
  - Moderately to severely active RA, in combination with MTX.
  - Active PsA, alone or in combination with MTX.
  - Active AS.

Approval Date: April 24, 2009

H. Other Clinical Uses Under Investigation

I. Pharmacology
SIMPONI is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα (a cytokine protein). There was no evidence of the SIMPONI antibody binding to other TNF superfamily ligands; in particular, the SIMPONI antibody did not bind or neutralize human lymphotoxin. SIMPONI does not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNFα is an important mediator of the articular inflammation that is characteristic of these diseases. SIMPONI modulated the *in*

vitro biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

J. Pharmacokinetics and Pharmacodynamics

Pharmacodynamics
In clinical studies, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix metalloproteinase 3 (MMP-3), intercellular adhesion molecule (ICAM)-1 and vascular endothelial growth factor (VEGF) were observed following SIMPONI administration with or without MTX in patients with RA, PsA and AS. These and other changes observed in specific study populations were consistent with an improvement in inflammatory disease process.

Pharmacokinetics
Following SC administration of SIMPONI to healthy subjects and patients with active RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg SIMPONI to healthy subjects produced a mean maximum serum concentration (C_{max}) of approximately 2.5 μg/mL. SIMPONI exhibited dose-proportional pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with active RA, mean systemic clearance of SIMPONI was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg. The volume of distribution for SIMPONI indicates that SIMPONI is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be approximately 2 weeks in healthy subjects and patients with RA, PsA or AS. By cross-study comparisons of mean AUC_{inf} values following an IV or SC administration of SIMPONI, the absolute bioavailability of SC SIMPONI was estimated to be approximately 53%.

When 50 mg SIMPONI was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by Week 12. With concomitant use of methotrexate, treatment with 50 mg SIMPONI SC every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4-0.6 μg/mL in patients with active RA, approximately 0.5 μg/mL in patients with active PsA, and approximately 0.8 μg/mL in patients with active AS. Patients with RA, PsA or AS who received concomitant MTX had approximately 67%, 25%, and 33% higher steady-state trough concentrations of SIMPONI than those who received SIMPONI in the absence of MTX. In the PsA and AS trials, the presence of concomitant MTX did not appear to influence clinical efficacy and safety parameters.

Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of SIMPONI.

Population PK analyses showed there was a trend toward higher apparent clearance of SIMPONI with increasing weight. However, across the PsA and AS populations, no meaningful differences in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-experienced and TNF-blocker-naïve patients did show evidence of a reduction in clinical efficacy with increasing body weight, but this effect was observed for both tested doses of SIMPONI (50 mg and 100 mg). Therefore, there is no need to adjust the dosage of SIMPONI based on patient's weight.

Population PK analyses suggest no PK differences between male and female patients after body weight adjustment in the RA and PsA trials. In the AS trial, female patients showed 13% higher apparent clearance than male patients after body weight adjustment. Subgroup

analyses based on gender showed that both female and male patients achieved clinically significant response at the proposed clinical dose. Dosage adjustment based on gender is not needed.

Populations PK analyses indicated that PK parameters of SIMPONI were not influenced by age in adult patients. Patients with age ≥65 years had apparent clearance of SIMPONI similar to patients with age <65 years. No ethnicity-related PK differences were observed between Caucasians and Asians, and there were too few patients of other races to assess for PK differences.

Patients who developed anti-SIMPONI antibodies generally had lower steady-state serum trough concentrations of SIMPONI.

No formal study of the effect of renal or hepatic impairment on the PK of SIMPONI was conducted.

K. Safety Information (Please see the enclosed prescribing information)

1.2 PLACE OF SIMPONI™ IN THERAPY

RHEUMATOID ARTHRITIS

A. Epidemiology and Relevant Risk Factors

Rheumatoid arthritis (RA) in the US has a prevalence of about 1% of the adult population, or about 1.3 million individuals (Helmick CG et al, 2008). The incidence of RA is less certain. Estimates from the Mayo Clinic found average annual incidence rates for persons aged 15 years and older to be 0.40 per 1000 males, 0.83 per 1000 for females, and 0.67 per 1000 overall (Hochberg, 1981; Lawrence et al, 1998). Women are 3 times more likely to be affected; about 1.5 million women and 600,000 men have RA. Almost 80% of RA cases occur in patients between the ages of 35 and 50 years (Kavanaugh and Lipsky, 1996). While the cause of RA remains unknown, the multiple contributing factors may include sex hormones, heredity, or infection (Kavanaugh and Lipsky, 1996; O'Dell JR, 2004; Schumacher et al, 1999).

B. Pathophysiology

The true underlying cause of RA remains unknown. Although a variety of immune and effector cells play a role in RA disease progression, macrophages may be of particular importance. Macrophage-derived cytokines, interleukin-1, and TNF-α, appear to play a critically important role in the induction and perpetuation of the chronic inflammatory process in the RA joints as well as the systemic manifestations of the disease (Grossman and Brahn, 1997).

TNF-α is at the apex of the complex cascade of immune-mediated events the result in the activation and propagation of numerous chemokines and effector cells, including osteoclasts, synoviocytes, and chondrocytes. This cascade of events results in immune and effector cell migration and invasion into the effected joint, producing inflammation and the synovitis characteristic of RA (Volin, 2000; Goronzy and Weyand, 2001). If left unchecked, this process can further result in bone resorption and cartilage degradation. The proliferating synovial tissue can form a pannus that extends over and sometimes through adjacent cartilage. This invasion may destroy significant amounts of cartilage and bone, producing joint space narrowing (JSN) and bone erosion (Breshnihan, 1999). Erosions can begin in the early stages of RA and progress throughout the course of the disease (Lane and Goldring, 1998).

C. Clinical Presentation

The main presenting symptoms of RA include pain aggravated by motion of joints, marked morning stiffness, swelling, and tenderness of the joints, which is typically symmetrical, and impaired physical functioning of the joints. Constitutional symptoms of RA include low-grade fever, weight loss and anorexia as well as fatigue, weakness, malaise, and sleep disturbance (Kavanaugh and Lipsky, 1996; Anderson, 2001).

Clinical features vary across patients and over time. Commonly involved joints include the hands, wrists, elbows, shoulders, cervical spine, hips, knees, feet, and ankles. Symmetrical arthritis may develop over weeks or months, typically initially involving the small joints of the hands and feet (Kavanaugh and Lipsky, 1996).

Significant joint damage can occur in the early stages of the disease. Magnetic resonance imaging (MRI) studies have identified joint erosions in 45% of joints of early RA patients who have been symptomatic for a median of 4 months (McQueen et al, 1998; McGonagle et al, 1999; Backhaus et al, 1999; Kraan, 1998). About 30% of RA patients demonstrate joint erosions within the first year after diagnosis and 70% within the first two to three symptomatic years (van der Heijde, 1995; Gremillion and van Vollenhoven, 1998). Very early joint changes seen in radiography can be associated with the level of destruction found 3 years later (Luukkainen et al, 1983). Research suggests that 50% of maximal radiological damage

occurs within the first 6 years of symptoms (Machold et al, 1998).

D. Approaches to Treatment – Principal Options / Practice Patterns

Conventional Drug Therapy

Traditional RA drug therapy is based on a stepped care approach where patients are initially treated with rest, exercise, physical and occupational therapies, and NSAIDs (Blackburn, 1996). This is followed by more aggressive treatment with nonbiologic DMARDs for the treatment of RA on the background of optimal and appropriate use of nonmedical therapies (i.e. physical and occupational therapies) as well as anti-inflammatory pharmacologic interventions (i.e. NSAIDs, intraarticular and oral corticosteroids) (Saag KG et al, 2008).

The ACR recommends nonbiologic DMARDs for patients with varying RA disease durations (i.e. <6 months, 6-24 months, and >24 months) (Saag KG et al, 2008). There are more than 170 possible dual-DMARD or triple-DMARD combinations among the 5 nonbiologic drugs considered by the ACR (i.e. hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine).

- Leflunomide or methotrexate. The initiation of methotrexate or leflunomide monotherapy is recommended for patients with all disease durations and for all degrees of disease activity.
- Hydroxychloroquine or minocycline. The initiation of hydroxychloroquine monotherapy was recommended for patients without poor prognostic features, with low disease activity, and with disease duration ≤24 months. Minocycline monotherapy was recommended for patients without poor prognostic features, with low disease activity, and with short disease duration.
- Sulfasalazine. As monotherapy, sulfasalazine is recommended for all patients with all disease durations, regardless of prognostic features, and with all degrees of disease activity.
- Dual-DMARD Combinations. Generally recommended for patients with moderate to high disease activity, regardless of disease duration or prognostic features.
- Triple-DMARD Combinations. Generally recommended for all patients with poor prognostic features and moderate or high levels of disease activity, regardless of disease duration.

The goals of RA treatment are to relieve the signs and symptoms, restore patient functioning, induce clinical remission, and inhibit the progression of joint destruction. Methotrexate (MTX), often considered the DMARD of choice, has been shown to achieve these goals to some extent; however, many patients have poor initial response to MTX and others may eventually lose response to this DMARD. Furthermore, patients may continue to have long-term radiographic progression with MTX (Kalden, 2001).

Biologic DMARDs

The advent of biologics has made for a significant advance in the therapeutic armamentarium for patients with RA. The ACR recommends the use of biologic DMARDs based on RA disease duration (i.e. <6 months, ≥6 months) in conjunction with disease activity (i.e. low to moderate disease activity for <6 months, or high disease activity for <3 months and for 3-6 months) (Saag KG et al, 2008).

- Anti-TNF agents in early RA. ACR recommends the use of anti-TNF agents (interchangeably) with methotrexate in patients with early RA to those who had never received DMARDs and had high disease activity. Patients with early RA and only low or moderate disease activity were not considered candidates for biologic therapy. The use of anti-TNF agents in combination with methotrexate was recommended if high disease activity was present for <3 months with features of both a poor prognosis and an absence of either barriers related to treatment cost and no insurance restrictions to accessing medical

care.

- Anti-TNF agents in intermediate- and longer-duration RA. The ACR recommends the use of anti-TNF agents (interchangeably) in patients for whom prior methotrexate monotherapy led to an inadequate response, with moderate disease activity and features of poor prognosis, and for patients with high disease activity, irrespective of prognostic features. Anti-TNF agents are also recommended (interchangeably) for patients in whom prior methotrexate therapy was used in combination, or if sequential administration of other nonbiologic DMARDs led to an inadequate response with at least moderate residual disease activity, regardless of prognostic features.

  The anti-TNF agents etanercept, infliximab, and adalimumab are efficacious in reducing the signs and symptoms of moderately to severely active RA, inhibiting the progression of structural damage, and improving physical function. Etanercept and adalimumab may be used alone or in combination with methotrexate; infliximab is used in combination with methotrexate (Enbrel® current prescribing information; Humira® current prescribing information; REMICADE® current prescribing information). SIMPONI, a new anti-TNF agent is indicated for the treatment of moderate to severely active RA in adults in combination with methotrexate (SIMPONI™ current prescribing information).

- Abatacept. The ACR recommended the use of abatacept in patients for whom methotrexate in combination with DMARDs or sequential administration of other nonbiologic DMARDs led to an inadequate response and with at least moderate disease activity and features of poor prognosis.

  Abatacept is indicated for moderately to severely active RA in adults, used as monotherapy or concomitantly with DMARDs other than TNF antagonists (Orencia® current prescribing information).

- Rituximab. The ACR recommended the use of rituximab in patients for whom methotrexate in combination with DMARDs or sequential administration of other nonbiologic DMARDs led to an inadequate response, and with high disease activity and features of poor prognosis.

  Rituximab is indicated in combination with MTX in adult patients with moderately to severely active RA who have an inadequate response to one or more TNF antagonists (Rituxan® current prescribing information).

- Biologic therapy combinations. The ACR did not recommend combination of biologic agents, based on data suggesting a higher rate of adverse events and/or lack of additive efficacy.

E. Alternative Treatment Options

Many providers refer RA patients for occupational and physical therapy evaluations early in the disease process when these kinds of therapies might be most helpful. Regular exercise may aid in maintaining strength, range of motion, and function (Ahern and Smith, 1997; Gremillion and van Vollenhoven, 1998).

F. Place and Anticipated Uses of Proposed Therapy in Treatment

SIMPONI has been extensively evaluated in several types of RA patients, including MTX-naïve, MTX inadequate responders, and patients previously treated with TNF antagonists. In the GO-BEFORE trial, MTX-naïve patients with moderately to severely active RA receiving SIMPONI plus MTX experienced significant improvement of signs and symptoms according to an ACR 50 response at week 24. The GO-FORWARD trial demonstrated that SIMPONI in combination with MTX also significantly improved signs and symptoms in patients who had failed MTX therapy, according to an ACR 20 response at week 14. The GO-AFTER trial demonstrated that SIMPONI plus MTX significantly improved signs and symptoms in

patients who were previously treated with ≥1 anti-TNF agent and discontinued treatment for any reason, according to an ACR 20 response at week 14.

G. Expected Outcomes of Therapy

SIMPONI, in combination with MTX, has been shown to improve RA signs and symptoms according to ACR responses, including tender and swollen joint count, pain, physician and patient global assessment scores, as well as disability index (HAQ-DI), and acute markers of inflammation, compared to MTX alone. SIMPONI + MTX efficacy in these parameters has been observed in MTX-naïve, MTX inadequate responders, and patients previously treated with ≥1 anti-TNF agent.

H. Other Key Assumptions and Rationale

Despite the currently available anti-TNF therapies for moderately to severely active RA, there is an ongoing need for additional treatment options. Further, recent reports indicate that patients who discontinue a TNF antagonist may benefit from another TNF antagonist (van Vollenhoven RF, 2007; Keystone EC, 2006). These reports, however, are from retrospective chart analyses, registries, and otherwise open-label studies (van Vollenhoven RF, 2007; Keystone EC, 2006; Villeneuve E et al, 2006). Prior to the GO-AFTER study, no adequately powered or controlled studies had been conducted to provide evidence of any efficacy or safety advantage related to using a TNF antagonist in RA patients who were previously treated with TNF antagonists (Smolen J et al, 2008). SIMPONI satisfies an unmet need for RA therapy that results in substantial relief of symptoms, a long-term maintenance effect with once monthly SC dosing, and a safety profile that is generally consistent with what is expected for an anti-TNF agent (Emery P et al, 2008; Keystone EC et al, 2008; Smolen J et al, 2008).

PSORIATIC ARTHRITIS

A. Epidemiology and Relevant Risk Factors

Psoriatic arthritis (PsA) is a chronic, inflammatory, usually rheumatoid factor (RF)-negative arthritis associated with psoriasis. According to a national survey, in the US an estimated 1 million adults suffer from PsA (National Psoriasis Foundation Benchmark Survey on Psoriasis and Psoriatic Arthritis, 2007). Affecting men and women equally, PsA peaks between the ages of 30 and 55 years.

B. Pathophysiology

TNF-α is considered a key inflammatory mediator that exhibits a wide variety of functional activities (Beutler et al, 1985). Overproduction of TNF-α appears to drive inflammation in a number of clinical conditions, and plays a role in psoriasis and PsA. Interactions between T-cells and monocytes/ macrophages, the primary source of proinflammatory cytokines, play a role in pathogenesis of PsA (Costello et al, 2001). Increased levels of TNF-α have been detected in joint fluid and tissues, and in psoriatic skin lesions in patients with PsA (Partsch et al, 1997; Ritchlin et al, 1998).

C. Clinical Presentation

PsA usually involves multiple peripheral joints, the axial skeleton, sacroiliac joints, fingernails, and entheses (Gladman et al, 1987). The presentation of PsA has been categorized into 5 overlapping clinical patterns, which include oligoarthritis, polyarthritis, arthritis of distal interphalangeal (DIP) joints, spondylitis, and arthritis mutilans (Gladman et al, 1987; Torre Alonso et al, 1991). Over one-third of patients with PsA also develop dactylitis and enthesopathy (Gladman et al, 1987; Sokoll et al, 2001). More than one-half of the patients with PsA may have evidence of erosions on x-rays, and up to 40% of the patients develop severe, erosive arthropathy (Torre Alonso et al, 1991; Gladman et al, 1987). PsA leads to functional impairment in a large proportion of patients, and increased mortality (Torre Alonso et al, 1991; Wong et al, 1997; Gladman et al, 1998) and, as such, is an important therapeutic challenge. Psoriasis skin involvement was reported to be associated with increased disability and reduced quality of life in patients with PsA comparable to what is observed in patients with RA, even in subjects with less radiologic damage (Sokoll et al, 2001). This underscores the necessity to effectively treat both arthritic and skin components of PsA to achieve optimized patient benefit.

D. Approaches to Treatment- Principle Options/Practice Patterns

Standard of Care

PsA is a unique disease entity whose 2 major presentations, arthritis and psoriasis, have a similar pathophysiology. Although patients with mild to moderate PsA may be treated with NSAIDs and/or intra-articular corticosteroids, the use of DMARDs, particularly MTX, along with biologic agents, are considered the standard of care with more significant PsA. In 2008, the AAD issued guidelines for the treatment of PsA, which discuss the use of DMARDs and biologic therapies in the treatment of patients with moderate to severe PsA. Further, according to the AAD guidelines, MTX, anti-TNF agents, or the combination of these therapies is considered first-line treatment for patients with moderate to severely active PsA (Gottlieb A et al, 2008).

Disease-Modifying Antirheumatic Drugs

According to the AAD, patients with moderate to severe PsA that is more extensive or aggressive in nature require therapy with DMARDs (Gottlieb A et al, 2008). Despite the progressive and potentially disabling nature of PsA, and in contrast to RA, only a few randomized, controlled trials have examined the role of traditional DMARDs in the treatment of PsA. The data supporting the use of MTX for the treatment of PsA is based on two randomized, placebo-controlled trials that were inadequately powered to assess clinical benefit; however, treatment with MTX resulted in a decrease in joint tenderness, swelling, and ESR (Black RL et al, 1964; Wilkens RF et al, 1984). Other DMARD have shown modest psoriatic efficacy (sulfasalazine, leflunomide) (Clegg DO et al, 1996; Kaltwasser JP et al, 2004). Other treatments,

such as antimalarials (e.g., hydroxychloroquine), cyclosporine, and gold, have all been employed in the management of PsA but have exhibited limited success (Gottlieb A et al, 2008).

Anti-TNF agents

Anti-TNF agents, including etanercept, adalimumab, and infliximab are currently approved by the FDA for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA. Anti-TNF agents are indicated for use alone or in combination with MTX (Enbrel current prescribing information; Humira current prescribing information; REMICADE current prescribing information).

SIMPONI has been evaluated for the treatment of active PsA in adults in a randomized, double-blind, placebo-controlled trial (GO-REVEAL). In this phase III study of 405 adult patients with active PsA, SIMPONI demonstrated significant improvement in the signs and symptoms of PsA (SIMPONI current prescribing information).

E. Alternative Treatment Options

Corticosteroids are rarely used to treat PsA since they have been reported to cause severe psoriasis flares upon withdrawal. NSAIDs reduce swelling and pain associated with the arthritic component of the disease, but may be associated with gastrointestinal problems over the long term. NSAIDs fail to improve psoriasis and some have been reported to induce lesion flares (Sendagorta et al, 1987).

F. Place and Anticipated Uses of Proposed Therapy in Treatment

SIMPONI is a new anti-TNF agent approved by the FDA for reducing signs and symptoms of active PsA in adults, alone or in combination with MTX.

G. Expected Outcomes of Therapy

Available data from a Phase III clinical trial (GO-REVEAL) including patients with active PsA who had an inadequate response to NSAIDs or DMARDs suggests that SIMPONI provides dramatic improvement in both arthritis and psoriasis symptoms. Substantial efficacy of SIMPONI in patients with PsA has been observed using a dose of 50 mg once monthly, with or without concomitant MTX. Results of this study indicates that SIMPONI, with or without concomitant MTX, significantly reduced clinical signs and symptoms of PsA (Kavanaugh A et al, 2009).

H. Other Key Assumptions and Rationale

Despite the currently available anti-TNF therapies for adults with active PsA, there is an ongoing need for additional treatment options. SIMPONI satisfies an unmet need for PsA therapy that results in substantial relief of joint and skin symptoms, a long-term maintenance effect with once monthly SC dosing, and a safety profile that is generally consistent with what is expected for an anti-TNF agent (Kavanaugh A et al, 2009).

ANKYLOSING SPONDYLITIS

A. Epidemiology and Relevant Risk Factors

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown etiology that involves the sacroiliac (SI) joints, axial skeleton, entheses, and peripheral joints. Chronic inflammation of entheses leads to new bone formation, syndesmophytes, and ankylosis of joints, primarily in the axial skeleton. It is this axial ankylosis that may lead to dramatic loss of range of motion and to disability. Patients with AS show similar amounts of disability, pain, and reduction in well being when compared with patients with rheumatoid arthritis (RA) (Zink et al, 2000). The disease may also have nonskeletal manifestations, including uveitis, carditis, pulmonary fibrosis, and cardiac conduction abnormalities. Considered a subset of the spondyloarthropathies, AS is strongly associated with the presence of the HLA-B27 genotype (van der Linden et al, 2005).

According to the Spondylitis Association of America (SAA), AS affects at least 1 in every 200 adults (approximately 0.5%) in the US, making it as common as rheumatoid arthritis. The disease usually affects young adults and commonly begins before the age of 35, and the prevalence in men is approximately three times that in women (Taurog JD, 2005; Spondylitis Association of America, www.spondylitis.org).

B. Pathophysiology

The immunopathology of reactive arthritis, of which AS and the spondyloarthropathies have some common characteristics, has been differentiated from RA (Simon et al, 1994; Yin et al, 1997). It appears that the reactive arthritides are dependent upon a T-helper cell (TH2) pathway, whereas RA is dependent upon TH1. Increased levels of interleukin (IL)-6, IL-10, tumor necrosis factor-α (TNF-α, and interferon-γ (IFN-γ) occur in AS (Lange et al, 2000; Claudepierre et al, 1997; Gratacos et al, 1994; Tutuncu et al, 1994). TNF-α probably plays a role in the sacroiliitis of AS similar to synovitis of RA. Five patients with active AS were evaluated with computed tomography-directed biopsies of their SI joints (Braun et al, 1995). Immuno-histologic analysis revealed T cells and macrophages in the cellular infiltrates. In situ hybridization studies of 3 subjects revealed abundant TNF-α.

C. Clinical Presentation

Although patients may experience a variety of musculoskeletal symptoms (proximal arthralgias, chest pain, tenderness around peripheral joints from enthesitis), the most common presenting symptom is low-back pain. The low-back pain usually begins before age 35, is insidious in onset, associated with morning stiffness, and, eventually, is symmetrical. These musculoskeletal symptoms may be associated with constitutional symptoms, such as fatigue, fever, and weight loss. In the most advanced cases, chronic inflammation leads to new bone formation on the spine, causing the spine to fuse in a fixed, immobile position (Spondylitis Association of America; www.spondylitis.org).

D. Societal and/or Economic Impact

Since AS usually starts at an early age, the socioeconomic impact of the disease on the patient and on society can be important. Most functional loss occurs during the first 10 years of illness in patients with severe involvement (Braun J et al, 2002). Sick leave, work disability and withdrawal from work are increased among patients with AS when compared to the general population. Older age at onset of disease, manual jobs or lower educational level and coping characterized by limiting or adapting activities are associated with withdrawal from work, while disease activity is a determinant of sick leave (Boonen A, 2002).

E. Approaches to Treatment – Principle Options/Practice Patterns

According to the ASAS/EULAR recommendations for the management of AS, treatment of AS should be tailored according to current manifestations of the disease (axial, peripheral, etc.) and level of current symptoms, clinical findings, and prognostic factors. Further, the optimal management of AS involves a combination of non-pharmacological and pharmacologic interventions. Non-pharmacological treatment of AS should include patient education and regular exercise. Individual

and group physical therapy should also be considered (Zochling J et al, 2006).

Conventional Therapy
Currently, the mainstay of treatment for patients with AS is limited to NSAIDs and physiotherapy. NSAIDs are recommended by the ASAS/EULAR as first-line drug treatment for patients with AS with pain and stiffness. In patients with increased GI risk, non-selective NSAIDs plus gastroprotective agents or selective COX-2 inhibitors (i.e. celecoxib) could be used (Zochling J et al, 2006). Few studies have been done with DMARDs, and DMARDs have not been proven to be clearly effective for axial disease. Sulfasalazine can influence the peripheral manifestations of the disease, but has minimal impact on axial disease and is effective only in some patients (Clegg et al, 1999; Leirisalo-Repo, 1998). Methotrexate (MTX) also has limited impact (Altan et al, 2001; Roychowdhury et al, 2002), and corticosteroids appear to be effective only in selected patients. Patients with severe disease may need phenylbutazone and opioids for pain relief.

Biologics
The advent of biologics has provided additional therapeutic options for physicians and patients with AS. The ASAS recommends anti-TNF treatment in patients with persistently high disease activity despite conventional treatments. There is no evidence to support the obligatory use of DMARDs before, or in combination with, anti-TNF treatment in patients with axial disease (Zochling et al, 2006).

F. Alternative Treatment Options
Analgesic agents such as acetaminophen and opioids may be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, or poorly tolerated. Additionally, corticosteroid injections may be considered; however, the use of systemic corticosteroids for axial disease is not supported by evidence (Zochling J et al, 2006). Alternatively, leflunomide, pamidronate, and thalidomide have been studied in AS with limited success (van Denderen et al, 2005; Maksymowych et al, 2002; Huang et al, 2002). Overall, these medications require further study.

Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal surgery is performed for a number of indications in AS, including disabling kyphosis, pain and/or segmental instability of spinal fractures, and less commonly, neurological complications such as spinal stenosis (Zochling et al, 2006).

G. Place and Anticipated Uses of Proposed Therapy in Treatment
SIMPONI is a new anti-TNF agent approved by the FDA for the treatment of active AS in adults.

H. Expected Outcomes of Therapy
Available data from a Phase III clinical trial (GO-RAISE) including adult patients with active AS despite current or previous NSAID or DMARD therapy suggests that SIMPONI provides dramatic improvement in spondylitis symptoms, including total back pain and morning stiffness as well as improvement in patient's global assessment of disease activity and physical function according to the BASFI. Substantial efficacy of SIMPONI in patients with AS has been observed using a dose of 50 mg once monthly. Results of this study indicate that SIMPONI significantly reduced clinical signs and symptoms of AS (Inman RD et al, 2008).

I. Other Key Assumptions and Rationale
Despite the currently available anti-TNF therapies for adults with active AS, there is an ongoing need for additional treatment options. SIMPONI satisfies an unmet need for AS therapy that results in substantial relief of symptoms, a long-term maintenance effect with once monthly SC dosing, and a safety profile that is generally consistent with what is expected for an anti-TNF agent (Inman RD et al, 2008).

2. SUPPORTING CLINICAL AND OUTCOMES INFORMATION

RHEUMATOID ARTHRITIS

2.1 SUPPORTING CLINICAL INFORMATION - SIMPONI IN RHEUMATOID ARTHRITIS

GO- BEFORE

Title
Golimumab, a new human anti-TNF-alpha monoclonal antibody, administered subcutaneously (SC) every 4 weeks in methotrexate-naive patients with active rheumatoid arthritis (RA): A randomized, double-blind, placebo-controlled, GO-BEFORE study (Emery P et al, abstract presented at EULAR 2008)

Date of Study
The GO-BEFORE study enrolled patients beginning 12 December 2005; the date of the last subject who completed the 24-week double-blind period was 1 October 2007.

Objectives
To assess the efficacy & safety of every 4 week SC administration of golimumab alone or in combination with MTX vs. MTX alone in MTX naïve patients with active RA.

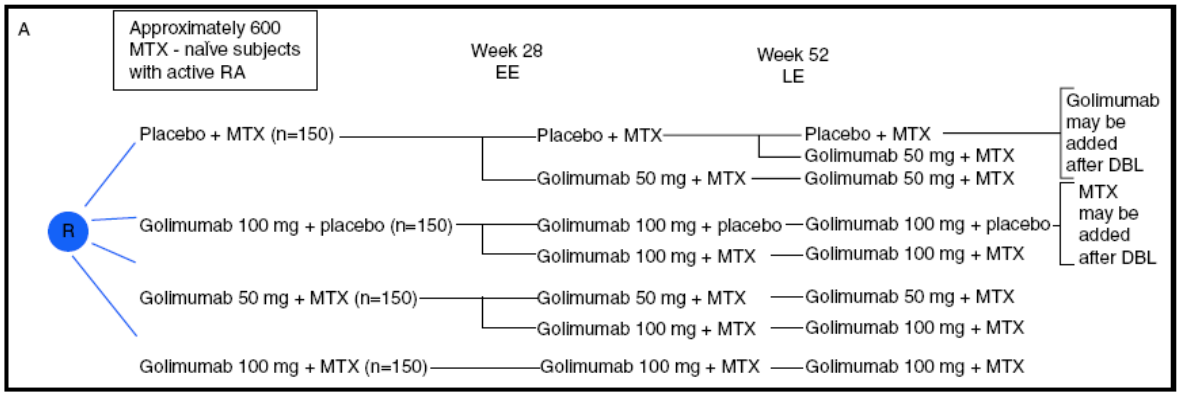
Methods
The efficacy and safety of SC golimumab alone or in combination with MTX in 637 MTX-naive patients with active RA (≥4 swollen and tender joints) was evaluated in a Phase III, randomized, double-blind, placebo-controlled study.

As shown in Figure 1, patients were randomized to receive:

- Placebo + MTX (n=160)
- Golimumab 100 mg + placebo (n=159)
- Golimumab 50 mg + MTX (n=159)
- Golimumab 100 mg + MTX (n=159)

Injections were administered every 4 weeks. The median MTX dose after week 8 was 20 mg/week. The primary endpoint was the proportion of patients who achieved 50% improvement according to the American College of Rheumatology (ACR) criteria (ACR 50) at week 24 in the combined golimumab + MTX groups versus placebo + MTX (intent-to-treat [ITT] analysis).

Figure 1. Study Design



EE = early escape (<20% improvement in both tender & swollen joint joints); R = randomization; LE = long-term extension; MTX = methotrexate; PE = primary endpoint (i.e. Week 24 – signs and symptoms according to ACR 50)

Results
At baseline, treatment groups were balanced for demographic and disease characteristics. The median RA duration ranged from 1.0 to 1.8 years, and median Disease Activity Score in 28 joints (DAS28; range 0–10) ranged from 4.980 to 5.148. Table 6 summarizes ACR and DAS28 responses through week 24 of the GO-BEFORE study.

There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). In the GO-BEFORE study, the golimumab monotherapy group was not statistically different from the MTX monotherapy groups in ACR responses.

Table 6. Summary of Efficacy Results at Week 24

Assessment	Placebo + MTX (n=160)	Golimumab 100 mg + placebo (n=159)	Golimumab 50 mg + MTX (n=159)	Golimumab 100 mg + MTX (n-159)	Combined Golimumab 50 mg/ 100 mg + MTX (n=318)
ACR 50 (primary endpoint; ITT) No. (%) [p]	47 (29.4%)	52 (32.7%) [p=0.521]	64 (40.3%) [p=0.042]	58 (36.5%) [p=0.177]	122 (38.4%) [p=0.053]
ACR 50 (primary endpoint; mITT) No. (%) [p]	47 (29.4%)	52 (33.1%) [p=0.473]	64 (40.5%) [p=0.038]	58 (36.5%) [p=0.177]	122 (38.5%) [p=0.049]
ACR 20 No. (%) [p]	79 (49.4%)	82 (51.6%) [p=0.677]	98 (61.6%) [p=0.028]	98 (61.6%) [p=0.028]	196 (61.6%) [p=0.011]
DAS28 (CRP) moderate/good response No. (%) [p]	97 (60.6%)	105 (66.0%) [p=0.310]	120 (75.5%) [p=0.005]	120 (75.5%) [p=0.004]	240 (75.5%) [p<0.001]
DAS28 (CRP) remission (<2.6) No. (%) [p]	45 (28.1%)	40 (25.2%) [p=0.572]	61 (38.4%) [p=0.050]	60 (37.7%) [p=0.069]	121 (38.1%) [p=0.031]
CRP Median % improvement (IQ range) [p]	43 (0,78)	25 (0,67) [p=0.268]	57 (3,83) [p=0.002]	63 (0,83) [p=0.014]	58 (0,83) [p=0.001]

Number (%) of patients who achieved endpoint or median (interquartile range [IQ]) % improved from baseline. All p values are versus placebo + MTX.
MTX = methotrexate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology; ITT = intent-to-treat; mITT = modified intent-to-treat (this analysis excludes 3 patients who were randomized but discontinued before receiving any treatment).

Safety

Through week 24, at least one SAE was reported in 6.9% of patients in the placebo + MTX group, 3.2% in the golimumab 100 mg + placebo group, 6.3% in the golimumab 50 mg + MTX group, and 6.3% in the golimumab 100 mg + MTX group. Serious infections were observed in 1.9%, 1.3%, 1.3%, and 4.4% of patients, respectively. One case of bone tuberculosis was reported in the golimumab 50 mg + MTX group. Further, 4 malignancies were reported (2 in the placebo + MTX group, 1 in the golimumab 50 mg + MTX group, and 1 in the golimumab 100 mg + MTX group), and 2 deaths occurred (1 suicide in the golimumab 50 mg + MTX group and 1 cardiac arrest after surgery in the golimumab 100 mg + MTX group).

GO-FORWARD

Title
A multicenter, randomized, double-blind, placebo-controlled trial of golimumab, a fully human anti-TNFα monoclonal antibody, administered subcutaneously, in subjects with active rheumatoid arthritis despite methotrexate therapy (Keystone EC et al, 2008)

Date of Study
The GO-FORWARD study enrolled patients beginning 21 February 2006; the date of the last subject who completed the 24-week double-blind period was 26 September 2007.

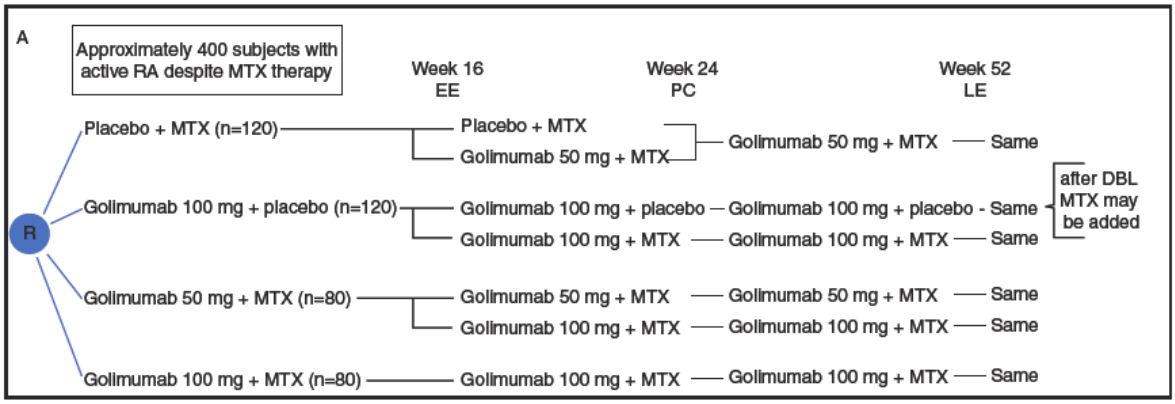
Objectives
The purpose of this study was to assess the efficacy of golimumab in subjects with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy as measured by American College of Rheumatology (ACR) 20 response at Week 14, and improvement from baseline in health assessment questionnaire (HAQ) at Week 24.

Methods
The efficacy and safety of SC golimumab in 444 patients with active RA (≥4 tender and swollen joints, plus at least 2 of the following: 1) C-reactive protein [CRP] ≥1.5 mg/dL or erythrocyte sedimentation rate [ESR] ≥28 mm/hr, 2) morning stiffness ≥30 minutes, 3) bone erosions, or 4) rheumatoid factor [RF] or anti-cyclic citrullinated peptide [CCP] positivity) despite MTX treatment was assessed in a 52–week, Phase III, randomized, double-blind, multi-center, placebo-controlled study. Patients enrolled in the 52–week, controlled portion of the study were eligible to continue in an open label extension up to 5 years.

As shown in Figure 2, patients were randomized to receive:
- Placebo + MTX (Group 1; n=133)
- Golimumab 100 mg + placebo (Group 2; n=133)
- Golimumab 50 mg + MTX (Group 3; n=89)
- Golimumab 100 mg + MTX (Group 4; n=89)

Subcutaneous injections were administered every 4 weeks. At week 16, non-responders (<20% improvement from baseline in both tender and swollen joint counts) from groups 1, 2, or 3 entered early escape in a double-blind manner. Patients originally randomized to group 1 received golimumab 50 mg, group 2 patients switched to active MTX, and group 3 patients switched to golimumab 100 mg. All other treatments were continued. The co-primary endpoints included the proportion of patients achieving 20% improvement according to the American College of Rheumatology criteria (ACR 20) at week 14 and improvement from baseline in the HAQ at week 24. Other endpoints included ACR 50/70/90 responses, ACR-N, the European League Against Rheumatism (EULAR) response, minimum clinically important difference in HAQ (improvement ≥0.25), remission according to the Disease Activity Score in 28 joints (DAS28) score <2.6, and sustained remission (DAS28 remission at week 14 and maintained through week 24).

Figure 2. Study Design



R = randomization; PC = placebo-crossover; EE = early escape (i.e. patients with <20% improvement in both tender & swollen joint counts); PE = primary endpoint (i.e. Week 14 – signs and symptoms according to ACR 20); LE = long-term extension; MTX = methotrexate

Results

At baseline, the groups well matched with regards to demographics and clinical characteristics. The median ages ranged from 50 – 52 years with median disease duration ranging from 4.5 – 6.7 years. The median swollen and tender joint counts ranged from 11 – 13 and 21 – 26, respectively. Further, patients had active disease (median DAS28 [ESR] range: 5.905 – 6.111) and impaired physical function (median HAQ range: 1.250 – 1.375). As shown in Table 3, golimumab + MTX was significantly better than MTX alone in improving signs and symptoms of RA according to ACR 20 responses. ACR 20 responses were observed in groups 3 and 4 as early as week 4. Additionally, golimumab + MTX significantly improved physical function according to the HAQ. At week 24, a minimum clinically important difference in HAQ (improvement ≥0.25) was achieved by 38.6%, 45.3%, 68.2%, and 72.1% of patients in groups 1, 2 (p=0.276), 3 (p<0.001), and 4 (p<0.001), respectively

At week 16, 31.6% (n=41), 27.1% (n=36), and 16.9% (n=15) of patients in groups 1, 2, and 3, respectively, were eligible for early escape. Of these, an ACR 20 response was achieved by 41.5% (n=17), 19.4% (n=7), and 20.0% (n=3) of patients at week 24, respectively. With respect to group 4, 15.7% (n=14) of patients were eligible for early escape at week 16 without any dose adjustments. At week 24, 28.6% (n=4) of these patients achieved an ACR 20 response.

No clear difference in the efficacy of the two golimumab dose groups that included concomitant MTX was evident. Patients who received golimumab without MTX also showed some evidence of benefit (e.g., ACR 50), but the proportion of patients with an ACR 20 response was not statistically significantly greater than that observed for patients who received MTX alone.

Table 3. Summary of Efficacy Results

Assessment	Placebo (n=133)	Golimumab 100 mg + placebo (n=133)	Golimumab 50 mg + MTX (n=89)	Golimumab 100 mg + MTX (n=89)	Combined Golimumab 50 mg/ 100 mg + MTX (n=178)
Co-Primary Endpoints					
ACR 20 at Week 14 No. (%) [p]	44 (33.1%)	59 (44.4%) [p=0.059]	49 (55.1%) [p=0.001]	50 (56.2%) [p<0.001]	99 (55.6%) [p<0.001]
HAQ (median improvement) at Week 24 Value (IQR) [p]	–0.13 (-0.38, 0.13)	–0.13 (-0.63, 0.25) [p=0.240]	–0.38 (-0.75, –0.13) [p<0.001]	–0.50 (-0.75, -0.13) [p<0.001]	–0.44 (-0.75, -0.13) [p<0.001]
Week 24					
ACR 20 No. (%) [p]	37 (27.8%)	47 (35.3%) [p=0.187]	53 (59.6%) [p<0.001]	53 (59.6%) [p<0.001]	106 (59.6%) [p<0.001]
ACR 50 No. (%) [p]	18 (13.5%)	26 (19.5%) [p=0.187]	33 (37.1%) [p<0.001]	29 (32.6%) [p<0.001]	62 (34.8%) [p<0.001]
ACR 70 No. (%) [p]	7 (5.3%)	15 (11.3%) [p=0.075]	18 (20.2%) [p<0.001]	13 (14.6%) [p=0.017]	31 (17.4%) [p=0.001]
ACR 90 No. (%) [p]	1 (0.8%)	3 (2.3%) [p=0.314]	5 (5.6%) [p=0.028]	2 (2.2%) [p=0.344]	7 (3.9%) [p=0.080]
ACR-N (median improvement) Value (IQR) [p]	0.00 (-25.00, 22.20)	0.00 (-25.40, 37.10) [p=0.151]	36.60 (0.00, 60.40) [p<0.001]	28.60 (0.00, 55.30) [p<0.001]	35.70 (0.00, 60.00) [p<0.001]
HAQ (median improvement) Value (IQR) [p]	–0.13 (-0.38, 0.13)	–0.13 (-0.63, 0.25) [p=0.240]	–0.38 (-0.75, -0.13) [p<0.001]	–0.50 (-0.75, -0.13) [p<0.001]	–0.44 (-0.75, -0.13) [p<0.001]
EULAR response (DAS28 calculated using ESR) No. (%) [p]	56 (42.1%)	69 (51.9%) [p=0.110]	64 (71.9%) [p<0.001]	68 (76.4%) [p<0.001]	132 (74.2%) [p<0.001]
DAS28 (ESR) remission No. (%) [p]	8 (6.0%)	16 (12.0%) [p=0.087]	18 (20.2%) [p=0.001]	20 (22.5%) [p<0.001]	38 (21.3%) [p<0.001]

Assessment	Placebo (n=133)	Golimumab 100 mg + placebo (n=133)	Golimumab 50 mg + MTX (n=89)	Golimumab 100 mg + MTX (n=89)	Combined Golimumab 50 mg/ 100 mg + MTX (n=178)
DAS28 (ESR) sustained remission No. (%) [p]	1 (0.8%)	8 (6.3%) [p=0.018]	9 (10.2%) [p=0.001]	10 (11.9%) [p<0.001]	19 (11.0%) [p<0.001]

All p values are versus placebo + MTX. MTX = methotrexate; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology; IQR = interquartile range; HAQ = Health Assessment Questionnaire

Safety

Through week 16, golimumab was generally well tolerated. The adverse events to week 24 are summarized in Table 4. There were no reported cases of tuberculosis, opportunistic infections, or lupus-like syndromes. One death was reported during the study. The patient, randomized to group 2, was hospitalized during week 8 after developing nausea, diarrhea, and dehydration. The patient developed an ileus and aspiration pneumonia and subsequently died due to sepsis a week later. Antibodies to golimumab were detected in 2.1% (5/236) of patients. None of these patients developed an injection-site reaction. Injection-site reactions were rarely reported and were mostly mild in intensity. Injection-site erythema, bruising, and warmth were the most commonly reported injection-site reactions. Further, there were no reported cases of severe or serious injection-site reactions, and none of the patients discontinued study treatment as a result of injection-site reactions.

Table 4. Summary of Safety Results through Week 24

Assessment	Placebo (n=134)	Golimumab 100 mg + placebo (n=133)	Golimumab 50 mg + MTX (n=212)	Golimumab 100 mg + MTX (n=105)
Adverse Events Event per PY (95% CI)	4.72 (4.16, 5.33)	2.74 (2.45, 3.05)	1.75 (1.53, 1.99)	2.82 (2.48, 3.19)
Serious Adverse Events Event per PY (95% CI)	0.09 (0.03, 0.21)	0.11 (0.06, 0.19)	0.08 (0.04, 0.14)	0.18 (0.10, 0.30)
Infections Event per PY (95% CI)	1.16 (0.89, 1.48)	0.71 (0.57, 0.88)	0.36 (0.27, 0.48)	0.79 (0.62, 1.00)
Serious Infections Event per PY (95% CI)	0.02 (<0.01, 0.10)	0.05 (0.02, 0.11)	0.02 (<0.01, 0.06)	0.08 (0.03, 0.17)
Injection-site Reactions Event per PY (95% CI)	0.11 (0.04, 0.24)	0.12 (0.06, 0.20)	0.08 (0.04, 0.14)	0.07 (0.03, 0.15)
Malignancies Event per PY (95% CI) [No; cancer site]	0.02 (<0.01, 0.10) [1; basal cell cancer]	0.02 (<0.01, 0.06) [2; squamous and basal cell cancer]	0.00 (0.00, 0.02) [0]	0.01 (<0.01, 0.06) [1; breast cancer]

GO-AFTER

Title
Golimumab, a new human anti-TNF-alpha monoclonal antibody, subcutaneously administered every 4 weeks in patients with active rheumatoid arthritis who were previously treated with anti-TNF-alpha agent(s): Results of the randomized, double-blind, placebo-controlled, GO-AFTER study (Smolen J et al, abstract presented at EULAR 2008)

Date of Study
The GO-AFTER study enrolled patients beginning 21 February 2006; the date of the last subject who completed the 24-week double-blind period was 26 September 2007.

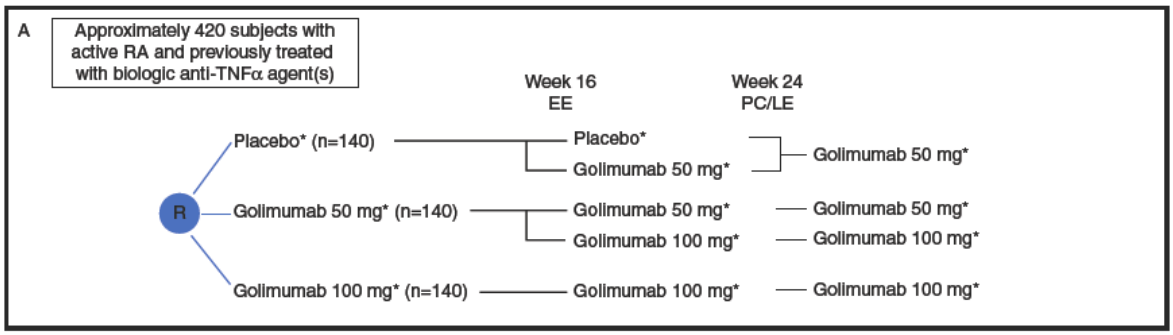
Objectives
The primary objective of this study was to evaluate the efficacy of SIMPONI in subjects with active RA who had been previously treated with biologic anti-TNF–α agent(s) by assessing the reduction in signs and symptoms of RA at Week 14.

Methods
Smolen et al evaluated the efficacy and safety of SC golimumab in 461 patients with active RA (≥4 tender and swollen joints) who had been previously treated with anti-TNF agent(s) in a Phase III, randomized, double-blind, placebo-controlled study.

As shown in Figure 3, patients were randomized to receive:
- Placebo (n=155)
- Golimumab 50 mg (n=153)
- Golimumab 100 mg (n=153)

Injections were administered every 4 weeks. Patients continued to receive stable doses of MTX, SSZ, and/or HCQ if receiving them at baseline. The primary endpoint included the proportion of patients achieving 20% improvement according to the American College of Rheumatology criteria (ACR 20) at week 14.

Figure 3. Study Design*



LE = long-term extension; PE = primary endpoint (i.e. Week 14 – signs and symptoms according to ACR 20 response); PC = placebo-crossover; R = randomization; DMARDs = disease-modifying antirheumatic drugs; EE = early escape (i.e. patients with <20% improvement from baseline in both tender & swollen joint counts)
*Patients may also be on background therapy, which includes (alone or in combination): methotrexate, sulfasalazine, hydroxychloroquine, oral corticosteroids, nonsteroidal anti-inflammatory drugs and analgesics

Results
At baseline, the median disease duration ranged from 8.65 to 9.80 years and 97% of patients were rheumatoid factor (RF) or anti-cyclic citrullinated peptide (anti-CCP) positive. Of note, 72% of patients were both RF and anti-CCP positive. Concomitant medications including MTX, SSZ, and HCQ were received by 66%, 5%, and 7% of patients, respectively. At least one previous anti-TNF agent had been received by all included patients, two previous anti-TNF agents had been received by 24.9% of patients, and three previous anti-TNF agents

had been received by 9.3% of patients. Reasons for discontinuation of prior anti-TNF agents included lack of efficacy (58.4%), intolerance (16.5%), or other (39.7%).

As shown in Table 1, golimumab 50 mg and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR and DAS28 responses, as well as improving physical function and fatigue according to the HAQ and FACIT-F, respectively. ACR 20 responders at week 14 among patients who discontinued previous anti-TNF therapy due to lack of efficacy included 35.7% and 42.7% of patients in the golimumab 50 mg and 100 mg groups, respectively, compared with 17.7% of patients in the placebo group (p=0.006, golimumab 50 mg vs. placebo; p<0.001, golimumab 100 mg vs. placebo).

Overall, there was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg).

Table 1. Summary of Efficacy Results

Assessment	Placebo (n=155)	Golimumab 50 mg (n=153)	Golimumab 100 mg (n=153)	Combined Golimumab 50 mg/ 100 mg (n=306)
Primary Endpoint				
ACR 20 at Week 14 No. (%)	28 (18.1%)	54 (35.3%)*	58 (37.9%)*	112 (36.6%)*
Week 24				
ACR 20 No. (%)	26 (16.8%)	52 (34.0%)*	67 (43.8%)*	119 (38.9%)*
ACR 50 No. (%)	8 (5.2%)	28 (18.3%)*	31 (20.3%)*	59 (19.3%)*
DAS28 (CRP) No. (%)	36 (23.2%)	75 (49.0%)*	98 (64.1%)*	173 (56.5%)*
DAS28 (ESR) No. (%)	38 (24.5%)	71 (46.4%)*	93 (60.8%)*	164 (53.6%)*
HAQ (median change from baseline) Value (IQ range)	0.0 (-0.3, 0.3)	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*
HAQ (≥0.25 change from baseline) No. (%)	53 (34.2%)	77 (50.3%)**	82 (53.6%)*	159 (51.9%)*
FACIT-F (mean change) Value ± SD	3.0 ± 9.7	6.0 ± 12.1†	7.5 ± 10.6*	6.8 ± 11.4*

All p values are versus placebo; *p<0.001; **p<0.01; †p<0.05. MTX = methotrexate; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints (based on EULAR moderate/good responders); ACR = American College of Rheumatology; HAQ = Health Assessment Questionnaire; IQ = interquartile range; SD = standard deviation; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue.

Safety

As shown in Table 2, ≥1 adverse event (AE) was observed in 72.3% of patients in the placebo group, compared with 66.4% to 78.3% of patients in the golimumab treatment groups. Through week 16, injection site reactions (ISRs) were reported in 2.6% of patients in the placebo group, compared with 3.9% and 10.5% of patients in the golimumab 50 mg and 100 mg groups, respectively. Erythema was the most commonly reported ISR. Serious or severe ISRs were not reported, and no ISRs led to treatment discontinuation.
In golimumab-treated patients, antibodies to golimumab were detected in 3.7% of patients. Concomitant MTX use did not appear to influence the development of antibodies.

Table 2. Summary of Safety Results at Week 24

Outcome	Placebo	Golimumab 50 mg	Golimumab 100 mg
Adverse Event (%)	72.3%	66.4%	78.3%
Serious Adverse Event (%)	9.7%	7.2%	4.6%
Serious Infections (%)	3.2%	3.3%	0.7%

PHASE II RA

Title
Golimumab in patients with active RA despite treatment with methotrexate (MTX) (Kay J et al, 2008)

Date of Study
The Phase II study enrolled patients beginning 01 December 2003.

Objectives
To assess the efficacy, safety, and pharmacology of subcutaneous administration of golimumab in patients with active rheumatoid arthritis (RA) despite treatment with MTX.

Methods
The efficacy, safety, and pharmacology of SC golimumab in 172 adults with active RA despite MTX treatment in a Phase II randomized, double-blind, placebo-controlled, dose-ranging study. Adult patients were eligible for inclusion if they met the ACR criteria for active RA and had a disease duration of ≥3 months. Patients were required to have ≥6 swollen joints and ≥6 tender joints and at least 2 of the following 3 criteria: CRP level ≥1.5 mg/dL, ESR of ≥28 mm/hour, and morning stiffness of ≥30 minutes. Patients were required to be on a stable dose of MTX (≥10 mg/week) for ≥3 months prior to enrollment, and were permitted to continue stable doses of oral corticosteroids (≤10 mg/day prednisone or equivalent) and/or nonsteroidal anti-inflammatory drugs (NSAIDs). Patients were randomized to receive the following study medication through week 20:

- Placebo every 2 weeks
- Golimumab 50 mg every 2 or 4 weeks
- Golimumab 100 mg every 2 or 4 weeks

At week 20, patients taking placebo were assigned to receive open-label REMICADE 3 mg/kg with induction followed by maintenance treatment every 8 weeks through week 44. All patients randomized to receive golimumab continued their assigned dose at a dosing interval of every 4 weeks through week 48. All patients continued stable doses of MTX (≥10 mg/week). The primary endpoint was an ACR 20 response at week 16 in the combined golimumab groups and at least one dose group when compared with placebo.

Results
ACR responses at week 16 and at week 52 as well as DAS28 responses using CRP or ESR are summarized in Table 7.

Table 7. Summary of Efficacy Results at Week 16 and 52

	PBO + MTX	GLM 50 mg q4wk + MTX	GLM 50 mg q2wk + MTX	GLM 100 mg q4wk + MTX	GLM 100 mg q2wk + MTX	Combined GLM + MTX
Week 16						
ACR 20 No. (%) [p]	13/35 (37.1%)	21/35 (60.0%) [p=0.056]	17/34 (50.0%) [p=0.119]	19/34 (55.9%) [p=0.119]	27/34 (79.4%) [p<0.001]	84/137 (61.3%) [p=0.010]
ACR 50 No. (%) [p]	2/35 (5.7%)	13/35 (37.1%) [p=0.001]	8/34 (23.5%) [p=0.009]	10/34 (29.4%) [p=0.009]	11/34 (32.4%) [p=0.005]	42/137 (30.7%) [p=0.003]
ACR 70 No. (%) [p]	0/35 (0%)	3/35 (8.6%) [p=0.077]	5/34 (14.7%) [p=0.018]	6/34 (17.6%) [p=0.009]	3/34 (8.8%) [p=0.072]	17/137 (12.4%) [p=0.028]
DAS28 (CRP) response (good/moderate)	19/35 (54.3%)	26/35 (74.2%)	23/34 (67.6%)	23/34 (67.7%)	29/34 (85.3%)	101/137 (73.7%
DAS28 (CRP) remission (<2.6)	2/35 (5.7%)	7/35 (20.0%) [p=0.074]	9/34 (26.5%) [p=0.019]	11/34 (32.4%) [p=0.005]	9/34 (26.5%) [p=0.019]	36/137 (26.3%) [p=0.009]
DAS28 (ESR) response (good/moderate)	15/35 (42.8%)	25/35 (71.5%)	22/34 (64.7%)	22/34 (64.7%)	29/34 (85.3%)	98/137 (71.5%)
DAS28 (ESR) remission (<2.6)	0/35 (0%)	2/35 (5.7%) [p=0.15]	4/34 (11.8%) [p=0.037]	3/34 (8.8%) [p=0.072]	4/34 (11.8%) [p=0.037]	13/137 (9.5%) [p=0.058]
Week 52						

	PBO + MTX	GLM 50 mg q4wk + MTX	GLM 50 mg q2wk + MTX	GLM 100 mg q4wk + MTX	GLM 100 mg q2wk + MTX	Combined GLM + MTX
ACR 20 No. (%)	-	21/28 (75.0%)	15/24 (62.5%)	19/26 (73.1%)	24/29 (80.8%)	79/107 (73.8%)
ACR 50 No. (%)	-	14/28 (50.0%)	9/24 (37.5%)	12/26 (46.2%)	13/29 (44.8%)	48/107 (44.9%)
ACR 70 No. (%)	-	7/28 (25.0%)	5/24 (20.8%)	7/26 (26.9%)	4/29 (13.8%)	23/107 (21.5%)
DAS28 (CRP) response (good/moderate)	-	26/28 (92.9%)	19/24 (79.2%)	23/26 (88.5%)	25/28 (89.3%)	93/106 (87.7%)
DAS28 (CRP) remission (<2.6)		8/28 (28.6%)	8/24 (33.3%)	10/26 (38.5%)	10/28 (35.7%)	36/106 (34.0%)

All p values are versus placebo + MTX. GLM = golimumab; MTX = methotrexate; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints; ACR = American College of Rheumatology

Safety

Through week 20, at least one AE was reported in 85.3% of placebo treated patients and 86.1% in the combined golimumab group. The most commonly reported AEs in the combined golimumab groups through week 20 included nausea, headache, injection-site erythema, and worsening of RA disease activity. Infections and injection site reactions were reported in 38.2% and 11.8% of placebo treated patients and 26.3% and 18.2% of all golimumab treated patients, respectively. SAEs were reported in 5.9% of patients in the placebo group and 8.8% in the combined golimumab group. Through week 52, the safety profile was similar to the placebo-controlled period. The most common infectious SAE reported in the golimumab treated patients was pneumonia (3 patients). Between weeks 20 and 52, serious noninfectious AEs in golimumab-treated patients included worsening of RA disease activity (3 patients), congestive heart failure (1 patient), cardiac tamponade (1 patient), lung cancer (1 patient with pre-existing abnormality on chest radiograph), squamous cell carcinoma (1 patient), and basal cell carcinoma (2 patients). There were no deaths or reports of tuberculosis or lymphoma following 52 weeks of treatment. One patient died from acute cardiac failure due to coronary insufficiency secondary to atherosclerotic cardiovascular disease 119 days after the last dose of golimumab.

2.1.1 Evidence Table - Clinical Studies in RHEUMATOID ARTHRITIS with SIMPONI

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
GO-BEFORE Emery, 2008 Phase III study in 637 moderately to severely active, MTX-naive RA patients	**Inclusion Criteria:** 1. Men and women 18 years of age or older with a diagnosis of RA (according to the revised 1987 criteria of the ACR for at least 3 months before the first administration of study agent. 2. Were MTX-naïve (had not received more than 3 weekly doses of MTX for RA at any time. 3. Had active RA as defined, for the purpose of this study, by persistent disease activity with ≥4 swollen and 4 tender joints at the time of screening and baseline and met ≥2 of the following 4 criteria: a. CRP ≥ 1.5 mg/dL at screening or erythrocyte sedimentation rate (ESR) by Westergren method of ≥ 28 mm in the first hour at screening or baseline b. Morning stiffness of ≥ 30 minutes at screening and baseline c. Bone erosion by x-ray and/or MRI prior to first administration of study agent d. Anti-CCP antibody-positive or RF positive at screening 4. Subjects were eligible to participate if they had no evidence of active TB and no history of latent TB on screening. Subjects with latent TB newly detected at screening were eligible if they were started on treatment for latent TB prior to or simultaneously with first study agent administration. 5. If using NSAIDs, other analgesics for RA, or oral corticosteroids, subjects must have been on a stable dose for at least 2	**Exclusion Criteria** 1. Subjects with other inflammatory diseases. 2. Subjects who had previously been treated with anti-TNFα therapy at any time and/or received disease DMARDs/ systemic immunosuppressives; intra-articular, IM, or IV corticosteroids; or anakinra within 4 weeks prior to the first study dose were to be excluded from participation. 3. Subjects who were pregnant or nursing, or who were planning pregnancy within 6 months after receiving the last administration of study agent. 4. Subjects who had a current serious infection or who, within 2 months prior to the first study dose, had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection. Subjects with chronic or recurrent infectious diseases or certain other medical conditions were also to be excluded.	**Co-Primary Endpoints:** • ACR 50 response at Week 24 • Change from baseline in van der Heijde Modified Sharp score at Week 52 Major Secondary Endpoints: • ACR 20 response at Week 24 • The proportion of subjects with abnormal CRP at baseline achieving an ACR 50 response at Week 24	• A greater percentage of SIMPONI-treated patients achieved ACR responses at week 14 and week 24. There was no clear evidence of improved ACR score with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). Further, the SIMPONI monotherapy group was not statistically different from the MTX monotherapy group in ACR response. • The proportion of patients achieving an ACR 50 response at week 24 was significantly greater in the SIMPONI 50 mg + MTX group (40%) versus MTX alone (29%; p=0.042).

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
	weeks prior to the first administration of study agent. If not using oral corticosteroids at the time of screening, the subject must not have received oral corticosteroids for at least 2 weeks prior to first administration of study agent.			
GO-FORWARD Keystone et al, 2008 Phase III study in 444 moderately to severely active RA patients despite MTX therapy	**Inclusion Criteria** 1. Were women or men of 18 years of age or older. 2. Had a diagnosis of RA (according to the revised 1987 criteria of the ARA; Arnett et al, 1988) for at least 3 months prior to screening. 3. Must have been treated with and tolerated MTX at a dose of at least 15mg/week for at least 3 months prior to screening and had a MTX dose of ≥15 mg/week and ≤25 mg/week and stable for at least 4 weeks prior to screening. 4. Had active RA as defined, for the purpose of this study, by persistent disease activity with ≥ 4 swollen and tender joints and at least 2 of the following 4 criteria: a. CRP ≥ 1.5 mg/dL at screening or ESR by Westergren method of ≥ 28 mm in the first hour at screening or baseline. b. Morning stiffness of ≥ 30 minutes at screening and baseline. c. Bone erosion by x-ray and/or by MRI prior to the first administration of study agent. d. Anti-cyclic citrullinated peptide (anti-CCP) antibody positive or RF-positive at screening.	**Exclusion Criteria** 1. Had inflammatory disease other than RA. 2. Had been treated with DMARDs/ systemic immunosuppressives other than MTX, or anakinra, during the 4 weeks prior to first administration of study agent, or previous treatment with anti-TNF agents. 3. Had received intra-articular, IM, or IV corticosteroids during the 4 weeks prior to first administration of the study agent. 4. Had a known hypersensitivity to human immunoglobulin proteins or other components of GLM. 5. Had received alefacept or efalizumab within 3 months prior to the first administration of the study agent. 6. Had used cytotoxic agents, including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents. 7. Had been treated with any investigational drug, including golimumab, within 5 half-lives of that drug prior to the first administration of the study agent. 8. Were pregnant, nursing, or planning a pregnancy or fathering a child within six months after receiving the last administration of study agent. 9. Had a history of latent or active	**Co-primary endpoints:** 1. ACR 20 response at Week 14 2. Change from baseline in HAQ at Week 24 **Other endpoints:** 1. ACR 50/70/90 responses and ACR-N 2. EULAR response 3. HAQ (improvement ≥0.25) 4. Remission according to the Disease Activity Score in 28 joints (DAS28) score <2.6) 5. Sustained remission (DAS28 remission at week 14 and maintained through week 24)	• The median ages ranged from 50 – 52 years with median disease duration ranging from 4.5 – 6.7 years. The median swollen and tender joint counts ranged from 11 – 13 and 21 – 26, respectively. • Patients had high disease activity at baseline (median DAS28 [ESR] range: 5.905 – 6.111) and impaired physical function (median HAQ-DI range: 1.250 – 1.375). • At week 14, an ACR 20 response was achieved by 33.1% of PBO + MTX-treated patients, 44.4% of GLM 100 mg + PBO-treated patients (p=0.059), 55.1% of GLM 50 mg + MTX-treated patients (p=0.001), and 56.2% of GLM 100 mg + MTX-treated patients (p<0.001). • At week 24, the median improvements from baseline in the HAQ-DI scores were –0.13, -0.13 (p=0.240), -0.38 (p=0.001), and -0.50 (p<0.001), respectively. • At week 24, clinical remission was achieved by 6%, 12% (p=0.087), 20.2% (p=0.001), and 22.5% (p<0.001), respectively. • Sustained remission was achieved by 0.8%, 6.3% (p=0.018), 10.2% (p=0.001), and 11.9% (p<0.001), respectively. • Through week 24 (Table 4), the rate of adverse events (AE) was 4.72, 2.74, 1.75, and 2.82 per patient-year (PY) in patients treated with PBO + MTX, GLM 100 mg + PBO, GLM 50 mg + MTX, and GLM 100 mg + MTX, respectively. The rates of serious AEs were 0.09, 0.11, 0.08, and 0.18 per PY, respectively.

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
	5. If using NSAIDS or other analgesics for RA, must have been on a stable dose for at least 2 weeks prior to the first administration of the study agent. 6. If using oral corticosteroids, must have been on a stable dose equivalent to a ≤10 mg of prednisone/day for at least 2 weeks prior to first administration of study agent. 7. Women of child bearing potential or men capable of fathering children must have been using adequate birth control measures during the study and for 6 months after receiving the last administration of study agent. 8. Were considered eligible according to TB screening criteria.	granulomatous infection, including TB, histoplasmosis, or coccidiomycosis. 10. Had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening. 11. Had a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB. 12. Had a nontuberculous mycobacterial infection or opportunistic infection (e.g., cytomegalovirus, *Pneumocystis carinii,* aspergillosis) within 6 months prior to screening. 13. Had received a live virus or bacterial vaccination within 3 months prior to the first administration of study agent. 14. Had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection within 2 months prior to first administration of study agent. 15. Were known to be infected with HIV, hepatitis B, or hepatitis C. 16. Had a history of known demyelinating diseases such as multiple sclerosis or optic neuritis. 17. Had current signs or symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease. 18. Had a history of, or concurrent, CHF, including medically controlled, asymptomatic CHF. 19. Had any known malignancy or had a history of malignancy within the		• The incidences of infections and serious infections were 1.16, 0.71, 0.36, and 0.79 per PY, respectively, and 0.02, 0.05, 0.02, and 0.08 per PY, respectively. • The rates of injection-site reactions were 0.11, 0.12, 0.08, and 0.07 per PY, respectively. • A total of 4 patients developed malignancies: 1 patient in group 1 (basal cell cancer), 2 patients in group 2 (squamous cell skin cancer and basal cell cancer), and 1 patient in group 4 (breast cancer). • There were no reported cases of TB, opportunistic infections, or lupus-like syndromes. Antibodies to golimumab were detected in 2.1% of patients. • One patient (group 2) died due to sepsis.

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
		previous 5 years (except nonmelonoma skin cancer). 20. Had a transplanted organ (with the exception of a corneal transplant performed >3 months prior to first study agent administration 21. Had a substance abuse (drug or alcohol) problem within the previous 3 years.		
GO-AFTER Smolen, 2008 Phase III study in 461 patients with moderately to severely active RA, previously treated with ≥1 anti-TNF agent	**Inclusion Criteria:** 1. Men or women 18 years of age or older with a diagnosis of RA for at least 3 months prior to screening. 2. Had active RA, defined as persistent disease activity with ≥4 swollen and tender joints, and must have documentation of previous treatment with at least 1 dose of a biologic anti-TNFα agent (i.e., etanercept, adalimumab, or infliximab) at least 12 weeks (infliximab) or 8 weeks (adalimumab or etanercept) prior to the first administration of study agent. 3. Subjects were to identify the reason (i.e., lack of efficacy, intolerance, or "other," which mainly included cost factors) for discontinuing prior anti-TNFα therapy. 4. The only DMARDs permitted during the study were: MTX, sulfasalazine, and hydroxychloroquine (alone or in combination). 5. Subjects who were receiving stable low doses of oral corticosteroids for at least 2 weeks prior to the first administration of the study agent and/or stable doses of NSAIDs for at least 2 weeks prior to the first administration of the study agent were also eligible for enrollment. 6. Subjects with a history of latent TB (i.e., had	**Exclusion Criteria** 1. Subjects excluded from the study were those with other inflammatory diseases. 2. Subjects were also excluded who had had a serious adverse reaction to an anti-TNFα agent, or if they had received any investigational anti-TNFα agent, or had received natalizumab, rituximab, or cytotoxic agents, including chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents at any time. 3. Subjects who were pregnant, nursing, or planning pregnancy within 6 months after receiving the last administration of study agent were to be excluded. 4. The study design excluded subjects who had a current serious infection or who, within 2 months prior to the first study dose, had had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection. 5. Subjects with chronic or recurrent infectious diseases or certain other medical conditions were also to be excluded, as were subjects with a history of known demyelinating	**Primary Endpoint**: ACR 20 response at week 14 Major Secondary Endpoints: • ACR 50 response at Week 14. • DAS28 (using CRP) response at Week 14. • ACR 20 response at Week 24. • Improvement from baseline in HAQ scores at Week 24.	• In the GO-AFTER trial, a greater percentage of patients treated with SIMPONI achieved ACR responses at week 14 and week 24. There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). • SIMPONI 50 mg and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3% and 37.9% vs. 18.1%, respectively; p<0.001) and Disease Activity Score in 28 joints (DAS28) responses using CRP (56.2% and 59.5% vs. 30.3%, respectively; p<0.001) or ESR (49.0% and 58.8% vs. 27.1%, respectively; p<0.001). • ACR 20 responders at week 14 among patients who discontinued previous anti-TNF therapy due to lack of efficacy included 35.7% and 42.7% of patients in the SIMPONI 50 mg and 100 mg groups, respectively, compared with 17.7% of patients in the placebo group (p=0.006, SIMPONI 50 mg vs. placebo; p<0.001, SIMPONI 100 mg vs. placebo). • At week 24, SIMPONI also improved physical function and fatigue according to

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
	a positive result from either the tuberculin skin test or the QuantiFERON-TB Gold test prior to screening) were allowed to enter the study provided they had completed an adequate treatment regimen for latent TB within 3 years prior to the first administration of study agent. Also permitted to enroll were subjects with evidence for newly detected (during screening) latent TB for which appropriate treatment had been initiated either prior to or simultaneously with the first administration of study agent. 7. In addition, subjects eligible for the study must have had serum ALT and AST levels at screening that did not exceed 1.5 times the ULN for the central laboratory conducting the test, and had hemoglobin concentrations ≥ 8.5 g/dL.	diseases, CHF, lymphoproliferative diseases, and malignancy (with the exception of a nonmelanoma skin cancer that has been treated with no evidence of recurrence).		the Health Assessment Questionnaire (HAQ) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores, respectively.
Phase II Kay, 2008 Phase II study in 172 patients with moderately to severely active RA despite MTX therapy	**Inclusion Criteria** • Men or women aged 18 years or older with a diagnosis of active RA according to the ACR for at least 3 months prior to screening who have not previously been treated with anti-TNF therapy. • Active RA as defined by persistent disease activity in subjects on a stable dose of at least 10mg/week MTX for the previous 4 weeks with at least 6 swollen and 6 tender joints and at least 2 of the following 3 criteria: 1. CRP ≥ 1.5 mg/dL 2. ESR by Westergren method of ≥ 28 mm/hour 3. Morning stiffness of ≥ 30 minutes • No history of significant MTX toxicity that would preclude continuation of MTX in this study. • Subjects must have tolerated a MTX dose	**See Inclusion Criteria**	ACR 20 at Week 16	• The study achieved its primary endpoint. A significantly greater proportion of patients in the combined golimumab plus MTX groups (61.3%) (p= 0.010) and in the group receiving 100 mg golimumab every 2 weeks (79.4%) (p< 0.001) had an ACR20 response at week 16 compared with patients in the placebo plus MTX group (37.1%). • When compared individually with the placebo group, the other 3 golimumab treatment groups did not show a statistically significant difference in the proportions of patients achieving an ACR20 response. However, each individual dose regimen had statistically significantly greater proportions of ACR50 responders. • Significantly greater proportions of patients in the combined golimumab plus MTX groups also achieved ACR50 and ACR70 responses at week 16, compared with the placebo plus MTX group. • ACR20, ACR50, and ACR70 responses were

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
	of at least 10 mg/week for at least 3 months prior to being treated with their first dose of study drug. • Subjects on stable, low doses of oral corticosteroids (not exceeding the equivalent of 10 mg of prednisone per day) and NSAIDs were eligible for enrollment.			observed as early as week 2 and were maintained through week 52, but there was no clear dose-response relationship.

2.2 OUTCOMES STUDIES – SIMPONI IN RHEUMATOID ARTHRITIS

Titles
Golimumab significantly improves self-reported productivity in patients with RA: Results from three phase III studies (Buchanan J et al, 2008)

Golimumab significantly reduces time lost from work for patients with RA: Pooled results from three phase III studies (Buchanan J et al, 2008)

Objectives
To evaluate the effect of golimumab on self-reported productivity and time lost from work in RA patients.

Methods
Impact on self-reported productivity and time lost from work for RA patients were prospectively evaluated through Week 24 in three phase III studies (GO-BEFORE, GO-FORWARD, GO-AFTER). Regarding self-reported productivity, at Weeks 0 and 24, patients were asked to indicate how much their disease affected their productivity at work, school or at home in the past4 weeks using a Visual Analog Scale (VAS 0 [did not affect productivity at all] to 10 [affected productivity very much]). Time lost from work was collected via questionnaire at baseline and every 8 weeks through Week 24.

- GO-BEFORE was a phase III, randomized, double–blind, placebo–controlled study of 637 MTX-naive patients with active RA (≥4 swollen and tender joints). See GO-BEFORE study description for more information.

- GO-FORWARD was a phase III, randomized, double-blind, placebo-controlled study of 444 patients with active RA (≥4 tender and swollen joints) despite MTX treatment. See GO-FORWARD study description for more information.

- GO-AFTER was a phase III, randomized, double–blind, placebo–controlled study of 461 patients with active RA (≥4 tender and swollen joints) who had been previously treated with ≥1 anti-TNF agent. See the GO-AFTER study description for more information.

Results
Phase III Rheumatoid Arthritis Studies — GO-BEFORE, GO-FORWARD, GO-AFTER
As shown in Table 8, golimumab significantly improved self-reported productivity in the GO-FORWARD and GO-AFTER studies. Further, in a pooled analysis of GO-BEFORE, GO-FORWARD, and GO-AFTER, golimumab significantly reduced time lost from work for patients with RA, compared to placebo.

Table 8. Improvement in Productivity Scores and Time Lost From Work through Week 24

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Combined Golimumab 50 mg / 100 mg
GO-BEFORE				
Patients Randomized	160	159	159	318
Baseline	6.4 ± 2.41	6.3 ± 3.29	6.4 ± 2.30	6.3 ± 2.34
Week 24 (mean ± SD change from baseline)	-2.27 ± 3.02	-2.48 ± 2.94	-2.90 ± 2.80	-2.69 ± 2.88
GO-FORWARD				
Patients Randomized	133	89	89	178
Baseline	5.4 ± 2.68	5.6 ± 2.73	5.7 ± 2.61	5.7 ± 2.66
Week 24 (mean ± SD change from baseline)	-0.45 ± 2.98	-1.97 ± 3.12 [p<0.001]	-2.00 ± 2.53 [p<0.001]	-1.99 ± 2.83 [p<0.001]
GO-AFTER				
Patients Randomized	155	153	153	306
Baseline	6.7 ± 2.32	6.7 ± 2.43	6.2 ± 2.45	6.4 ± 2.44
Week 24 (mean ± SD	-0.52 ± 2.79	-1.77 ± 2.90	-2.10 ± 2.92	-1.93 ± 2.91

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Combined Golimumab 50 mg / 100 mg
change from baseline)		[p<0.001]	[p<0.001]	[p<0.001]
Pooled (GO-BEFORE, GO-FORWARD, GO-AFTER)				
Patients Randomized	448	399	400	799
Week 16 Time lost from work by patients (n; mean ± SD days) [p]	n=206; 5.0 ± 13.9	n=184; 3.9 ± 15.9 [p=0.001]	n=196; 3.3 ± 13.5 [p=0.009]	n=380; 3.6 ± 14.7 [p<0.001]
Week 24 Time lost from work by patients (n; mean ± SD days) [p]	n=211; 6.9 ± 19.7	n=188; 5.2 ± 20.5 [p=0.004]	n=202; 4.8 ± 18.3 [p=0.041]	n=390; 5.0 ± 19.4 [p=0.004]

Title
Golimumab significantly improves physical function, health-related quality of life, and fatigue in rheumatoid arthritis patients: Results from the GO-FORWARD study (Genovese MC et al, 2008)

Date of Study
See GO-FORWARD study description.

Objectives
To evaluate the impact of golimumab on physical function, health-related quality of life (HR-QoL) and fatigue in patients with active RA despite MTX therapy.

Method
In this analysis, the impact of golimumab treatment on HR-QoL and fatigue was evaluated in patients enrolled in the GO-FORWARD trial (see GO-FORWARD study description). HR-QoL and fatigue were assessed according to the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the Short Form-36 (SF-36), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire, respectively.

Results
As shown in Table 10, golimumab 50 mg or 100 mg + MTX significantly improved fatigue and the PCS score of the SF-36 through week 24. Additionally, treatment with golimumab 100 mg + MTX was significantly better than MTX alone in improving the MCS score of the SF-36 at week 14 and 24.

Table 10. HR-QoL and Fatigue Results at Week 14 and 24

Assessment	Placebo + MTX (n=133)	GLM 100 mg + Placebo (n=133)	GLM 50 mg + MTX (n=89)	GLM 100 mg + MTX (n=89)	Combined GLM 50 mg / 100 mg + MTX (n=178)
Week 14					
SF-36 PCS (mean change) Value ± SD [p]	2.4 ± 7.8	4.7 ± 8.8 [p<0.05]	8.0 ± 7.2 [p<0.001]	7.4 ± 8.0 [p<0.001]	7.7 ± 7.6 [p<0.001]
SF-36 MCS (mean change) Value ± SD [p]	1.6 ± 9.8	3.5 ± 11.4	1.6 ± 11.0	4.6 ± 10.2 [p<0.05]	3.1 ± 10.7
FACIT-F (mean change) Value ± SD [p]	2.3 ± 9.2	6.0 ± 10.8 [p<0.05]	7.6 ± 8.9 [p<0.001]	6.4 ± 9.6 [p<0.05]	7.0 ± 9.3 [p<0.001]
Week 24					
SF-36 PCS (mean change) Value ± SD [p]	2.5 ± 8.1	4.7 ± 8.8	8.3 ± 8.3 [p<0.001]	7.0 ± 7.8 [p<0.001]	7.7 ± 8.1 [p<0.001]
SF-36 MCS (mean change) Value ± SD [p]	0.8 ± 9.7	3.4 ± 10.2 [p<0.05]	1.8 ± 10.9	4.3 ± 10.7 [p<0.05]	3.1 ± 10.8 [p<0.05]
FACIT-F (mean change) Value ± SD [p]	2.2 ± 9.5	5.6 ± 10.5 [p<0.05]	7.3 ± 8.6 [p<0.001]	7.2 ± 8.6 [p<0.001]	7.2 ± 8.6 [p<0.001]

All p values are versus placebo + MTX. GLM = golimumab; MTX = methotrexate; SD = standard deviation; SF-36 PCS = Physical Component Summary of Short-Form (SF)-36; SF-36 MCS = Mental Component Summary of SF-36; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue.

Title
Golimumab significantly improves physical function and fatigue in RA patients previously treated with anti-TNF-α agents: Results from the GO-AFTER study (Kay J et al, 2008)

Date of Study
See GO-AFTER study description.

Objectives
To evaluate the effect of golimumab on physical function & fatigue in patients with active RA previously treated with anti-TNFα agent(s).

Method
In this analysis, the impact of golimumab treatment on physical function according to HAQ and fatigue according to the FACIT-F questionnaire was evaluated in patients enrolled in the GO-AFTER trial (see GO-AFTER study description).

Results
As shown in Table 9, golimumab 50 mg or 100 mg + MTX significantly improved fatigue at weeks 14 and 24, and HAQ scores through week 24.

Table 9. Summary of FACIT-F and HAQ Scores through Week 24 in the GO-AFTER Trial

Assessment	Placebo (n=155)	Golimumab 50 mg (n=153)	Golimumab 100 mg (n=153)	Combined Golimumab 50 mg/ 100 mg (n=306)
Week 14				
FACIT-F (mean change) Value ± SD	2.2 ± 9.6	6.4 ± 10.2*	6.3 ± 10.4*	6.3 ± 10.3*
Week 24				
HAQ (median change from baseline) Value (IQ range)	0.0 (-0.3, 0.3)	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*
HAQ (≥0.25 change from baseline) No. (%)	53 (34.2%)	77 (50.3%)**	82 (53.6%)*	159 (51.9%)*
FACIT-F (mean change) Value ± SD	3.0 ± 9.7	6.0 ± 12.1†	7.5 ± 10.6*	6.8 ± 11.4*

*p < 0.001; ** p <0.05

2.2.1 Evidence Table. Outcomes Studies in RHEUMATOID ARTHRITIS with SIMPONI

Study Design	Inclusion / Exclusion Criteria	Endpoints	Results
Pooled (GO-AFTER, GO-FORWARD, GO-BEFORE) Buchanan, 2008 Prospective evaluation through Week 24	See GO-AFTER, GO-FORWARD, GO-BEFORE Study Design (2.1)	Self-reported productivity; time lost from work	See nested table below

	Placebo	Golimumab 50 mg	Golimumab 100 mg	Combined Golimumab 50 mg / 100 mg
GO-BEFORE				
Patients Randomized	160	159	159	318
Baseline	6.4 ± 2.41	6.3 ± 3.29	6.4 ± 2.30	6.3 ± 2.34
Week 24 (mean ± SD change from baseline)	-2.27 ± 3.02	-2.48 ± 2.94	-2.90 ± 2.80	-2.69 ± 2.88
GO-FORWARD				
Patients Randomized	133	89	89	178
Baseline	5.4 ± 2.68	5.6 ± 2.73	5.7 ± 2.61	5.7 ± 2.66
Week 24 (mean ± SD change from baseline)	-0.45 ± 2.98	-1.97 ± 3.12 [p<0.001]	-2.00 ± 2.53 [p<0.001]	-1.99 ± 2.83 [p<0.001]
GO-AFTER				
Patients Randomized	155	153	153	306
Baseline	6.7 ± 2.32	6.7 ± 2.43	6.2 ± 2.45	6.4 ± 2.44
Week 24 (mean ± SD change from baseline)	-0.52 ± 2.79	-1.77 ± 2.90 [p<0.001]	-2.10 ± 2.92 [p<0.001]	-1.93 ± 2.91 [p<0.001]
Pooled (GO-BEFORE, GO-FORWARD, GO-AFTER)				
Patients Randomized	448	399	400	799
Week 16 Time lost from work by patients (n; mean ± SD days) [p]	n=206; 5.0 ± 13.9	n=184; 3.9 ± 15.9 [p=0.001]	n=196; 3.3 ± 13.5 [p=0.009]	n=380; 3.6 ± 14.7 [p<0.001]
Week 24 Time lost from work by patients (n; mean ± SD days) [p]	n=211; 6.9 ± 19.7	n=188; 5.2 ± 20.5 [p=0.004]	n=202; 4.8 ± 18.3 [p=0.041]	n=390; 5.0 ± 19.4 [p=0.004]

Study Design	Inclusion / Exclusion Criteria	Endpoints	Results
GO-FORWARD Genovese, 2008	See GO-FORWARD study description (2.1)	HAQ, Fatigue, and SF-36 at Weeks 14 and 24	

Assessment	Placebo + MTX (n=133)	GLM 100 mg + Placebo (n=133)	GLM 50 mg + MTX (n=89)	GLM 100 mg + MTX (n=89)	Combined GLM 50 mg / 100 mg + MTX (n=178)
Week 14					
SF-36 PCS (mean change) Value ± SD [p]	2.4 ± 7.8	4.7 ± 8.8 [p<0.05]	8.0 ± 7.2 [p<0.001]	7.4 ± 8.0 [p<0.001]	7.7 ± 7.6 [p<0.001]
SF-36 MCS (mean change) Value ± SD [p]	1.6 ± 9.8	3.5 ± 11.4	1.6 ± 11.0	4.6 ± 10.2 [p<0.05]	3.1 ± 10.7
FACIT-F (mean change) Value ± SD [p]	2.3 ± 9.2	6.0 ± 10.8 [p<0.05]	7.6 ± 8.9 [p<0.001]	6.4 ± 9.6 [p<0.05]	7.0 ± 9.3 [p<0.001]
Week 24					
SF-36 PCS (mean change) Value ± SD [p]	2.5 ± 8.1	4.7 ± 8.8	8.3 ± 8.3 [p<0.001]	7.0 ± 7.8 [p<0.001]	7.7 ± 8.1 [p<0.001]
SF-36 MCS (mean change) Value ± SD [p]	0.8 ± 9.7	3.4 ± 10.2 [p<0.05]	1.8 ± 10.9	4.3 ± 10.7 [p<0.05]	3.1 ± 10.8 [p<0.05]
FACIT-F (mean change) Value ± SD [p]	2.2 ± 9.5	5.6 ± 10.5 [p<0.05]	7.3 ± 8.6 [p<0.001]	7.2 ± 8.6 [p<0.001]	7.2 ± 8.6 [p<0.001]

Study Design	Inclusion / Exclusion Criteria	Endpoints	Results
GO-AFTER Kay, 2008	See GO-AFTER study description (2.1)	HAQ at Week 24; Fatigue at Weeks 14 and 24	

Assessment	Placebo (n=155)	Golimumab 50 mg (n=153)	Golimumab 100 mg (n=153)	Combined Golimumab 50 mg/ 100 mg (n=306)
Week 14				
FACIT-F (mean change) Value ± SD	2.2 ± 9.6	6.4 ± 10.2*	6.3 ± 10.4*	6.3 ± 10.3*
Week 24				
HAQ (median change from baseline) Value (IQ range)	0.0 (-0.3, 0.3)	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*	0.3 (0.0, 0.5)*
HAQ (≥0.25 change from baseline) No. (%)	53 (34.2%)	77 (50.3%)**	82 (53.6%)*	159 (51.9%)*
FACIT-F (mean change) Value ± SD	3.0 ± 9.7	6.0 ± 12.1†	7.5 ± 10.6*	6.8 ± 11.4*

*p < 0.001; ** p <0.05

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2. SUPPORTING CLINICAL AND OUTCOMES INFORMATION

PSORIATIC ARTHRITIS

2.3 CLINICAL STUDIES - SIMPONI IN PSORIATIC ARTHRITIS

GO-REVEAL

Title
Golimumab, a new human tumor necrosis factor α antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study (Kavanaugh A et al, 2009)

Golimumab, a new human, TNF alpha antibody administered subcutaneously every 4 weeks in psoriatic arthritis patients: 52-week efficacy and safety results of the randomized, placebo-controlled GO-REVEAL study (Kavanaugh A et al, 2008)

Date of Study
The GO-REVEAL study enrolled patients beginning 12 December 2005; the date of the last subject who completed the 24-week double-blind period was 14 May 2007.

Objectives
The primary objective of this trial was to evaluate the efficacy of SC injections of golimumab in subjects with active psoriatic arthritis (PsA) by assessing reduction in signs and symptoms of PsA.

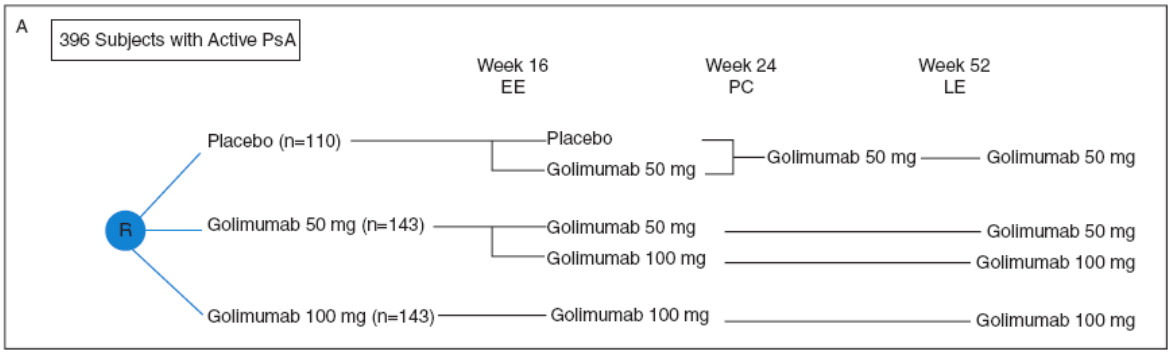
Methods
The safety and efficacy of golimumab in reducing signs and symptoms of active PsA and associated skin and nail disease was evaluated in a Phase III, multicenter, randomized, placebo-controlled clinical trial. Eligible adult patients had at least 3 or more swollen and tender joints, negative rheumatoid factor (RF), at least 1 subset of PsA, and the presence of plaque psoriasis with a qualifying lesion at least 2 cm in diameter.

As shown in Figure 4, patients were randomly assigned to receive SC injections every 4 weeks of:

- Placebo (n=113)
- Golimumab 50 mg (n=146)
- Golimumab 100 mg (n=146)

At week 16, patients who did not experience an adequate arthritis response (<10% improvement from baseline in both the swollen and tender joint counts) entered early escape, with dose escalation to golimumab 50 mg (placebo patients) or golimumab 100 mg (golimumab 50 mg patients) in a blinded manner. Patients in the golimumab 100 mg group meeting early escape criteria continued with the 100 mg dose in a blinded manner. Beginning at week 24, all patients received golimumab and continued to receive SC treatment every 4 weeks. Concomitant use of methotrexate was allowed but not required. The primary endpoint of the study was a ≥20% improvement in the ACR criteria for clinical improvement (ACR 20) at week 14. Major secondary endpoints included an ACR 20 response at week 24, PASI75 at week 14 in patients with at least 3% BSA affected by psoriasis at baseline, HAQ scores at week 24, and SF-36 PCS scores at week 14.

Figure 4. Study Design



R = randomized; PC = placebo crossover; LE = long-term extension; EE = early escape (i.e. patients with <10% improvement in both tender & swollen joint counts); PE = primary endpoint (i.e. Week 14 – signs and symptoms according to ACR 20 response)

Results

A total of 405 patients (mean age range of 45.7–48.2 years) with active PsA despite therapy with DMARDS or NSAIDs were enrolled. Patients enrolled in the study had a mean swollen joint count of 12.0–14.1, a mean tender joint count of 21.9–24.0, mean CRP levels of 1.3–1.4, and mean PASI scores of 8.4–11.1. SIMPONI-treated patients experienced significantly improved signs and symptoms of active PsA and associated psoriatic skin and nail disease, compared with patients in the placebo group through 24 weeks of therapy (Table 1). There were no major differences observed in the efficacy profiles of the golimumab 50 mg or golimumab 100 mg dosages. ACR 20 responses at week 14 were observed with both SIMPONI doses irrespective of concomitant MTX use (p=0.66). Patients switching from golimumab 50 mg to golimumab 100 mg had minimal improvement from week 16 to 24 (14% achieved an ACR 20 response, 4% achieved an ACR 50 response, 0% achieved an ACR 70 response). A larger proportion of placebo-treated patients who switched to golimumab 50 mg in early escape achieved ACR responses at week 24 (47% achieved an ACR 20 response, 14% achieved and ACR 50 response, and 6% achieved and ACR 70 response). Significant improvements in enthesitis were seen in SIMPONI 50 mg- and 100 mg-treated patients, compared with placebo; however, significant improvements in dactylitis were only observed with the SIMPONI 100 mg dose, compared with placebo.

All patients remaining on placebo at week 20 received SIMPONI 50 mg at week 24 and through week 52. Treatment with SIMPONI 50 mg and 100 mg every 4 weeks improved active PsA and associated skin disease through week 52 (Table 11). Statistical comparisons of efficacy at week 52 were not performed.

Table 11. Proportion of Patients Achieving Clinical Response to Golimumab Therapy Through Week 52

	Placebo (n=113)	Golimumab 50 mg (n=146)	Golimumab 100 mg (n=146)
Primary Endpoint			
ACR 20 (%)	9	51*	45*
Week 24			
ACR 20 (%)	12	52*	61*
ACR 50 (%)	3.5	32.2*	37.7*
ACR 70 (%)	0.9	18.5*	21.2*
HAQ score, mean ± SD change	-0.01	0.33*	0.39*
PsARC responders (%)	29	70*	85*
DAS28 (CRP) responders	24	64*	78*
Dactylitis score (median % change)	42%	100¶	100%*
Enthesitis score – PsA modified MASES (median % change)	12	60*	67*
Morning stiffness, mean ± SD change	-20.4 ± 257.7	-67.2 ± 231.1*	-90.1 ± 234.5*
PASI 75# (%)	1	56*	66*
PASI 90# (%)	0	32*	32*
NAPSI score (median % change)	0	33*	54*
Week 52**			
ACR 20 (%)	-	78.4	74.1
ACR 50 (%)	-	56.9	0.45
ACR 70 (%)	-	43.1	52.6
HAQ score (mean change)	-	0.49	31.3
DAS28 responders	-	92.8	86.0
PASI75 (%)	-	62.0	69.3

*p<0.001; †p=0.015; ‡p=0.1; §p=0.009; ¶p=0.08.
#Among the 74% of patients (217/292) in whom ≥3% of the BSA was affected by psoriasis at baseline.

**SIMPONI 50 mg: For week 52, only patients randomized to golimumab 50 mg and who did not enter early escape are included. Golimumab 100 mg: For week 52, all patients randomized to golimumab 100 mg are included, regardless of whether they entered early escape.

Safety

Through week 24, 65% (222/343) of all golimumab-treated patients and 59% (67/113) of placebo-treated patients experienced adverse events (AEs). Nasopharyngitis and upper respiratory tract infection were the most frequently reported AEs. Serious adverse events (SAEs) were reported in 2% (7/343) of all patients receiving golimumab, compared to 6% (7/113) of patients receiving placebo. Serious infections were reported in more placebo-treated patients (4%; 4/113) than patients treated with golimumab (<1%; 2/343). No cases of active tuberculosis were observed. Three malignancies were reported in the golimumab 100 mg group; none were reported in any other treatment group through week 24. Injection site reactions (ISRs) occurred in 3% (10/343) of patients in the all golimumab group and in 3% (3/113) of patients in the placebo group. No ISRs were considered severe, serious, or resulted in discontinuation of treatment, and no patient experienced anaphylactic or serum sickness-like reactions. The incidence of antibodies to golimumab occurred in 4.6% of all patients treated with golimumab; the presence of antibodies had no impact on ACR 20 responses or ISRs. Post-baseline liver transaminase level elevations occurred more frequently in patients treated with golimumab compared to placebo. Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred in 24% (33/135) and 18% (26/143) of patients receiving golimumab 50 mg, 35% (47/133) and 13% (18/142) of patients receiving golimumab 100 mg, and 18% (18/98) and 10% (11/107) of patients receiving placebo, respectively. Concomitant treatment with MTX had no affect on transaminase levels.

Through week 52, 4.6% of patients (all receiving golimumab) experienced SAEs. ISRs occurred in 7.6% of all golimumab-treated patients. There were no reports of tuberculosis or opportunistic infections. Additional safety events were reported (including during the long-term extension after week 52 of treatment) and included 4 additional malignancies (colon cancer, small cell lung cancer, and 2 cases of basal cell carcinomas). Two patients died (small cell lung cancer and a climbing accident) and one case of liver histoplasmosis was reported in the golimumab 100 mg group.

2.3.1 Evidence Table. SIMPONI Clinical Studies in PSORIATIC ARTHRITIS

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
GO-REVEAL Kavanaugh, 2009 Phase III study in 405 patients with active PsA despite DMARD or NSAID therapy	**Inclusion Criteria:** • Men and women 18 years of age or older if, for at least 6 months prior to first study agent administration, they had a diagnosis of PsA and had active PsA despite current or previous DMARD or NSAID therapy. • Diagnosis of active PsA must have included the presence of arthritis (characterized by 3 or more swollen joints and 3 or more tender joints) and psoriasis (defined as plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter and not on axilla, inframammary area, or groin). • Subjects must have had at least 1 of the PsA subsets (distal interphalangeal [DIP] joint arthritis, polyarticular arthritis with the absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, and spondylitis with peripheral arthritis). • Subjects were eligible to participate if they had no evidence of active TB and no history of latent TB on TB screening. Subjects with latent TB newly detected at screening were eligible if they were started on treatment for latent TB prior to or simultaneously with first study agent administration. • Subjects who had used or were currently using MTX, NSAIDS, oral corticosteroids, or topical or systemic psoriasis treatments were eligible for enrollment provided they met treatment-specific requirements.	**Exclusion Criteria:** • The study design excluded subjects with other inflammatory diseases that could confound the evaluations of benefit from golimumab therapy. • Subjects who had previously been treated with anti-TNF therapy, received systemic immunosuppressives, DMARDs other than MTX, or systemic corticosteroids within 4 weeks prior to the first study dose were excluded from participation. Subjects who had received certain other drugs were also excluded. • Subjects who were pregnant, nursing, or planning pregnancy within 6 months after receiving the last administration of study agent were to be excluded. • The study design excluded subjects who had a current serious infection or who, within 2 months prior to the first study dose, had had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection.	ACR 20 at week 14	• Golimumab 50 mg ± MTX, compared with placebo ± MTX, resulted in a significant improvement in signs and symptoms as demonstrated by the proportion of patients with an ACR 20 response at week 14 (51% vs. 9%; p<0.001). There was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). • Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. • ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. • Among the 74% of patients in whom at least 3% of the BSA was affected by psoriasis at baseline, 40% of those in the golimumab 50 mg group and 58% of those in the golimumab 100 mg group achieved a PASI75 response at week 14, compared with 3% of placebo-treated patients (p<0.001 for both doses). • Significant improvements were observed for other endpoints such as HAQ scores at week 14 and SF-36 PCS scores at week 14 also.

2.4 OUTCOMES STUDIES – SIMPONI IN PSORIATIC ARTHRITIS

Title
Golimumab significantly improves physical function, health-related quality of life, productivity, and reduces time lost from work for caregivers in patients with active psoriatic arthritis (Mease P et al, 2008)

Date of Study
See GO-REVEAL study description

Objectives
To evaluate the impact of golimumab injections every 4 weeks on physical function, self-reported productivity, health-related quality of life (HR-QoL), and time lost from work for caregivers in patients with active psoriatic arthritis.

Methods
GO-REVEAL was a phase III, randomized, double-blind, placebo-controlled study that evaluated the impact of golimumab on signs and symptoms of active PsA (≥3 swollen and tender joints) and associated skin and nail disease. A total of 405 patients were randomized to receive SC injections of placebo, golimumab 50 mg, or golimumab 100 mg. Injections were administered every 4 weeks. Concomitant use of methotrexate was allowed but not required. The primary endpoint of the study was the proportion of patients achieving an ACR 20 response at week 14.

Results
Phase III Psoriatic Arthritis Study — GO-REVEAL
Impact on self-reported productivity and time lost from work for caregivers were prospectively evaluated through Week 24 in the GO-REVEAL study in PsA patients. Self-reported productivity was measured using a VAS scale (0 cm = not at all affected, to 10 cm = affected very much). As shown in Table 12, golimumab significantly improved productivity scores and reduced time lost from work (days) by caregivers through week 24 for golimumab versus placebo.

Table 12. Improvement in SF-36, HAQ, Productivity Scores, and Time Lost From Work by Caregivers through Week 24

	Placebo	Golimumab 50 mg	Golimumab 100 mg
Baseline			
PCS score (mean ± SD)	31.9 ± 9.3	33.0 ± 10.7	32.8 ± 8.9
MCS score (mean ± SD)	47.6 ± 10.7	45.4 ± 12.2	45.0 ± 11.7
HAQ (mean ± SD)	1.0 ± 0.6	1.0 ± 0.7	1.1 ± 0.6
Week 14			
PCS score (mean ± SD)	0.63 ± 7.7	6.53 ± 8.9*	7.85 ± 9.6*
MCS score (mean ± SD)	0.40 ± 11.4	2.79 ± 10.3†	3.56 ± 12.1†
HAQ score (mean ± SD)	0.044 ± 0.4	0.312 ± 0.5*	0.378 ± 0.5*
HAQ (>0.3 unit change from baseline, %)	25.7%	39.3%†	52.5%*
Week 24			
PCS score (mean ± SD)	0.67 ± 8.7	7.42 ± 9.2*	8.22 ± 9.6*
MCS score (mean ± SD)	-0.60 ± 12.1	3.37 ± 10.6†	4.29 ± 11.1†
HAQ score (mean ± SD)	-0.013 ± 0.5	0.331 ± 0.6*	0.331 ± 0.6*
HAQ (>0.3 unit change from baseline, %)	22.1%	43.2%*	51.7%*
Productivity (mean ± SD change from baseline)	-0.1 ± 2.6	-1.9 ± 2.7*	-2.6 ± 3.0*
Time (days) lost from work by caregivers (mean ± SD change from baseline	1.1 ± 4.0	0.2 ± 1.0‡	0.2 ± 1.3§

PCS = physical component summary; MCS = mental component summary; HAQ = Health Assessment Questionnaire; SD = standard deviation; *p<0.001; †p<0.05; ‡p=0.047; §p=0.023.

2.4.1 Evidence Table. SIMPONI Outcomes Studies in PSORIATIC ARTHRITIS

Study Design	Inclusion /Exclusion Criteria	Endpoints	Results
GO-REVEAL Kavanaugh, 2009 Phase III study in 405 patients with active PsA despite DMARD or NSAID therapy	See GO-REVEAL study design (2.1)	• Physical function was assessed using the HAQ disability index • HR-QoL by using the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores • The proportion of patients achieving ≥0.3 improvement in HAQ, the minimal clinically important difference (MCID) for PsA • Self-reported productivity was measured on VAS scale (0 cm = not affected, to 10 cm = affected very much) • Cumulative time lost from work (days) for caregivers	See table below

	Placebo	Golimumab 50 mg	Golimumab 100 mg
Baseline			
PCS score (mean ± SD)	31.9 ± 9.3	33.0 ± 10.7	32.8 ± 8.9
MCS score (mean ± SD)	47.6 ± 10.7	45.4 ± 12.2	45.0 ± 11.7
HAQ (mean ± SD)	1.0 ± 0.6	1.0 ± 0.7	1.1 ± 0.6
Week 14			
PCS score (mean ± SD)	0.63 ± 7.7	6.53 ± 8.9*	7.85 ± 9.6*
MCS score (mean ± SD)	0.40 ± 11.4	2.79 ± 10.3†	3.56 ± 12.1†
HAQ score (mean ± SD)	0.044 ± 0.4	0.312 ± 0.5*	0.378 ± 0.5*
HAQ (>0.3 unit change from baseline, %)	25.7%	39.3%†	52.5%*
Week 24			
PCS score (mean ± SD)	0.67 ± 8.7	7.42 ± 9.2*	8.22 ± 9.6*
MCS score (mean ± SD)	-0.60 ± 12.1	3.37 ± 10.6†	4.29 ± 11.1†
HAQ score (mean ± SD)	-0.013 ± 0.5	0.331 ± 0.6*	0.331 ± 0.6*
HAQ (>0.3 unit change from baseline, %)	22.1%	43.2%*	51.7%*
Productivity (mean ± SD change from baseline)	-0.1 ± 2.6	-1.9 ± 2.7*	-2.6 ± 3.0*
Time (days) lost from work by caregivers (mean ± SD change from baseline	1.1 ± 4.0	0.2 ± 1.0‡	0.2 ± 1.3§
*p<0.001; †p<0.05; ‡p=0.047; §p=0.023.			

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2. SUPPORTING CLINICAL AND OUTCOMES INFORMATION

ANKYLOSING SPONDYLITIS

2.5 CLINICAL STUDIES - SIMPONI IN ANKYLOSING SPONDYLITIS

GO-RAISE

Title
Efficacy and safety of golimumab in patients with ankylosing spondylitis: Results of a randomized, double-blind, placebo-controlled, Phase III trial (Inman RD et al, 2008)

Date of Study
The GO-RAISE study enrolled patients beginning 13 December 2005; the date of the last subject who completed the 24-week double-blind period was 15 May 2007.

Objectives
The primary objective of the GO-RAISE study was to evaluate the efficacy and safety of golimumab in reducing the signs and symptoms of active AS.

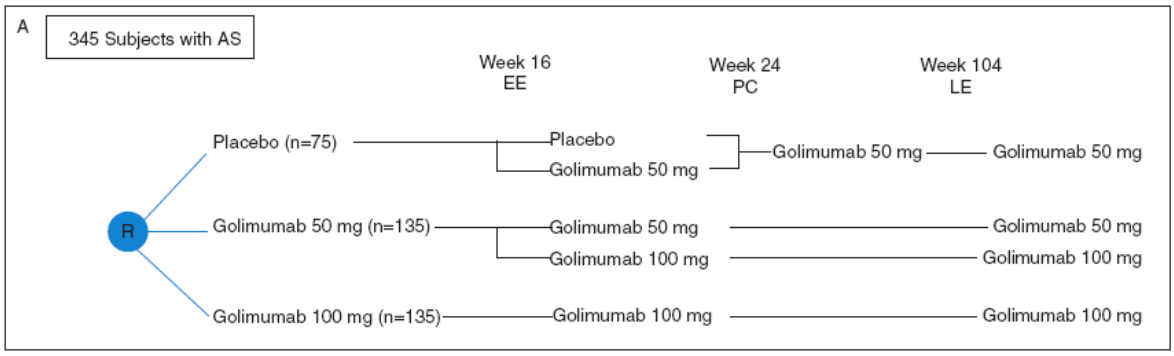
Methods
The efficacy and safety of golimumab for the treatment of patients with active AS was evaluated in a Phase III, randomized, double-blind, placebo-controlled clinical trial. Patients were eligible for inclusion in the study if they had AS according to the modified New York Criteria for ≥3 months, a BASDAI (0–10) score of ≥4, a spinal back pain score of ≥4 (VAS; 0–10) scoring system, and an inadequate response to current or previous NSAIDs or DMARDs. Patients were permitted to continue concomitant MTX, SSZ, HCQ, corticosteroids, and NSAIDs at stable doses. Patients receiving placebo or golimumab 50 mg who had <20% improvement from baseline in both total back pain and morning stiffness measures entered early escape in a double-blind fashion at week 16 (patients in the placebo group received golimumab 50 mg and patients in the golimumab 50 mg group received golimumab 100 mg). All other patients remained on their previous medication until week 24.

As shown in Figure 5, patients were randomly assigned to receive SC injections every 4 weeks of:

- Placebo (n=78)
- Golimumab 50 mg (n=138)
- Golimumab 100 mg (n=140)

The primary efficacy endpoint was the proportion of patients with ≥20% improvement in the ASsessment in AS International Working Group criteria (ASAS 20) at week 14. Secondary endpoints included ASAS 40, ASAS partial remission, and 20% improvement in 5 of 6 ASAS domains (ASAS 5/6). Other endpoints included assessments of disease activity according to the BASDAI, back pain VAS, night pain VAS, patient's global assessment and CRP level, an assessment of physical function according to the BASFI, assessments of range of motion according to the BASMI and chest expansion, assessment of health-related quality of life according to SF-36, and an assessment of sleep according to the JSEQ.

Figure 5. Study Design



LE = long-term extension; EE = early escape (i.e. patients with <20% improvement in both total back pain and morning stiffness); PE = primary endpoint (i.e. week 14 – signs and symptoms according to ASAS 20 response); PC = placebo-crossover; R = randomization

Results

Baseline demographics and disease characteristics were similar among the three treatment groups. Based on baseline demographic and disease characteristics, patients had active disease with moderately high levels of pain and inflammation as evidenced by baseline disease activity values. As noted in Table 13, both golimumab regimens resulted in statistically significant improvement in the signs and symptoms of AS, as measured by ASAS responses, compared to placebo. The proportion of patients achieving an improvement in ASAS 20 response at week 14 was 59.4% and 60.0% for the golimumab 50 mg and 100 mg groups, respectively, compared with the placebo group (21.8%; p<0.001 for both comparisons). ASAS 20 responses were achieved by greater proportions of patients in the golimumab groups at the first assessment, 4 weeks after the first SC injection. Except for the change from baseline in BASMI score, all other predefined endpoints were achieved at week 14 and maintained through week 24

A total of 66 patients entered early escape at week 16 (41 patients, placebo/golimumab 50 mg; 25 patients, golimumab 50 mg/golimumab 100 mg). At week 24, 50.0% and 16.0% of patients achieved an ASAS 20 response in the placebo/golimumab 50 mg and golimumab 50 mg/golimumab 100 mg groups, respectively.

Overall, no clear difference in efficacy was evident between the golimumab 50-mg and 100-mg dose groups through week 24.

Table 13. Summary of Clinical Efficacy

Assessment	Placebo (n=78)	Golimumab 50 mg (n=138)	Golimumab 100 mg (n=140	Golimumab Combined (n=278)
Primary Endpoint				
ASAS 20	21.8%	59.4%*	60.0%*	59.7%*
Week 24				
ASAS 20	23.1%	55.8%*	65.7%*	60.8%*
ASAS 40	15.4%	43.5%*	54.3%*	48.9%*
ASAS 5/6	12.8%	49.3%*	50.7%*	50.0%*
BASDAI 50	14.7%	50.8%*	47.8%*	49.3%*
BASFI (0 – 10)	0.4 (-1.1, 1.3)	–1.6 (-3.4, 0.0)*	–1.6 (-3.5, –0.3)*	–1.6 (-3.5, –0.2)*
BASMI (0 – 10)	0.0 (-1.0, 0.0)	0.0 (-1.0, 0.0)	–0.2 (–1.0, 0.0)	0.0 (-1.0, 0.0)
SF-36 PCS score (0 – 50)	2.0 (-2.4, 7.7)	7.9 (1.1, 17.6)*	8.1 (2.1, 15.0)*	8.1 (2.0, 16.6)*
SF-36 MCS score (0 – 50)	–0.3 (-3.2, 6.3)	1.4 (-3.3, 6.6)	5.2 (-2.3, 12.8)§	2.9 (-2.8, 9.7)‡
JSEQ (0–20 scale)	–1.0 (-3.0, 1.0)	–3.0 (-6.0, 0.0)*	–4.0 (-7.0, 0.0)*	–3.0 (-6.0, 0.0)*

*p<0.001; †p=0.002; ‡p<0.05; §p<0.01

Safety

Through week 24, ≥1 adverse event was reported in 79.9% of all golimumab-treated patients and 76.6% of placebo-treated patients, and 4.7% and 6.5% of patients, respectively, had ≥1 serious adverse event. There

was an increased incidence of infections in patients treated with golimumab 50 mg (46.4%) and golimumab 100 mg (48.6%), compared with patients receiving placebo (36.4%). Serious infections were reported in 3 patients: 1 placebo-treated patient (gastrointestinal inflammation) and 2 golimumab 100 mg-treated patients (mononucleosis and chronic otitis media). Injection site reactions were reported in 8.7%, 6.4%, and 2.6% of patients, respectively. None of these were considered to be serious. Antibodies to golimumab were detected in 4.1% of patients through week 24. Two patients, 1 in the placebo group and 1 in the golimumab 100 mg group, developed a malignancy; both had basal cell carcinoma. There were no deaths, opportunistic infections, or cases of tuberculosis reported.

2.5.1 Evidence Table. SIMPONI Clinical Studies in ANKYLOSING SPONDYLITIS

Study Design	Inclusion Criteria	Exclusion Criteria	Endpoints	Results
GO-RAISE Inman, 2008 Phase III study in 356 patients with active AS despite current or previous DMARD or NSAID therapy	Inclusion Criteria: • Men and women 18 years of age or older were eligible to participate if, for at least 3 months prior to the first administration of study agent, they had a diagnosis of definite AS, as defined by the 1984 Modified New York Criteria. • A diagnosis of AS must have included both a radiographic criterion and at least 1 of the following clinical criteria: o Low back pain and stiffness for more than 3 months, which improves with exercise, but is not relieved by rest, o Limitation of motion of the lumbar spine in both the sagittal and frontal planes, o Limitation of chest expansion relative to normal values corrected for age and sex. • Subjects were eligible to participate if they had neither shown evidence of active TB nor a history of latent TB on TB screening. • Subjects with latent TB newly detected during screening were eligible if they were started on TB prophylactic treatment prior to or simultaneously with the first study agent administration. • Subjects on stable doses of MTX, SSZ, HCQ, corticosteroids and/or NSAIDs were permitted.	Exclusion Criteria: • Subjects with inflammatory diseases other than AS that might confound the evaluation of benefit from the golimumab therapy, including but not limited to, RA, psoriatic arthritis, systemic lupus erythematosus, or Lyme disease. • Subjects who were pregnant, nursing, or planning a pregnancy within 6 months of receiving the last administration. • The study design excluded subjects who had a current serious infection or who, within 2 months prior to the administration of the first study dose had had a serious infection, had been hospitalized for an infection, or had been treated with IV antibiotics for an infection. • Subjects with chronic or recurrent infectious diseases or certain other medical conditions were also to be excluded. • The study design excluded subjects with prior exposure to a biologic anti-TNF agent.	ASAS 20 at week 14	• Golimumab + DMARDs, compared with placebo + DMARDs resulted in a significant improvement in signs and symptoms as demonstrated by ASAS 20 responses at week 14 (59% vs. 22%; $p \leq 0.001$). • There was no clear evidence of improved ASAS response with the higher golimumab dose group (100 mg) compared to the lower SIMPONI dose group (50 mg). • All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group vs. the placebo group at week 14.

2.6 OUTCOMES STUDIES – SIMPONI IN ANKYLOSING SPONDYLITIS

Title
Golimumab significantly improves productivity in patients with active ankylosing spondylitis: Results from the Phase 3 GO-RAISE study (Braun J et al, 2008)

Is there a relationship between functionality and productivity in patients with active ankylosing spondylitis? Results from the GO-RAISE study (Parasuraman S et al, 2008)

Date of Study
See GO-RAISE study description

Objectives
To evaluate the impact of golimumab on productivity in patients with active AS.

Methods
Phase III Ankylosing Spondylitis Study — GO-RAISE
GO-RAISE was a phase III, multicenter, randomized, placebo-controlled study that evaluated the impact of golimumab on signs and symptoms of active AS (BASDAI ≥4 and back pain score ≥4). A total of 356 patients were randomly assigned to receive SC injections of golimumab 50 mg, golimumab 100 mg or placebo at baseline and every 4 weeks thereafter. The primary efficacy endpoint was the proportion of patients with an ASAS 20 response at week 14. Impact on self-reported productivity was prospectively evaluated through Week 24 in the GO-RAISE study in AS patients. Self-reported productivity was assessed at Weeks 16 and 24 using a VAS scale (0 cm = not at all affected, to 10 cm = affected very much).

Results
As shown in Table 14, significant improvements in productivity scores after golimumab treatment were achieved at Week 16 and maintained through week 24. Additionally, the relationship between physical function according to the BASFI and productivity was assessed at Week 24. In all patients, there was a positive correlation between change from baseline in BASFI and productivity scores ($r=0.67$, $p<0.0001$). Further, a regression model revealed that 1 unit change in BASFI resulted in a change of 0.86 unit in the productivity VAS scale ($r^2 = 0.47$, $p<0.0001$).

Table 14. Improvement in Productivity Scores through Week 24

	Placebo (n=78)	Golimumab 50 mg (n=138)	Golimumab 100 mg (n=140)
Baseline Productivity (VAS 0 – 10, mean ± SD)	6.3 ± 2.5	6.6 ± 2.5	6.8 ± 2.3
Week 16 Productivity (VAS 0 – 10, mean ± SD change from baseline)	-0.4 ± 2.7	-2.8 ± 3.0*	-2.9 ± 2.9*
Week 24 Productivity (VAS 0 – 10, mean ± SD change from baseline)	-0.4 ± 2.7	-2.7 ± 3.1*	-2.9 ± 3.0*

*p<0.001

2.6.1 Evidence Table. SIMPONI Outcomes Studies in ANKYLOSING SPONDYLITIS

Study Design	Inclusion / Exclusion Criteria	Endpoints	Results
GO-RAISE Parasuraman, 2008 Phase III study in 356 patients with active AS despite current or previous DMARD or NSAID therapy	See GO-RAISE study design (2.1)	Self-reported productivity at Week 16 and 24	

	Placebo (n=78)	Golimumab 50 mg (n=138)	Golimumab 100 mg (n=140)
Baseline Productivity (VAS 0 – 10, mean ± SD)	6.3 ± 2.5	6.6 ± 2.5	6.8 ± 2.3
Week 16 Productivity (VAS 0 – 10, mean ± SD change from baseline)	-0.4 ± 2.7	-2.8 ± 3.0*	-2.9 ± 2.9*
Week 24 Productivity (VAS 0 – 10, mean ± SD change from baseline)	-0.4 ± 2.7	-2.7 ± 3.1*	-2.9 ± 3.0*
*p<0.001			

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3.0 MODELING REPORT

3.0 MODELING REPORT

This report summarizes an excel-based budget impact model. An interactive version of the models can be presented upon request.

3.1 Budget Impact Model

3.1.1 Overview

The objective of the excel-based budget impact model (BIM) was to estimate the pharmacy budget and financial impact of formulary adoption and uptake of SIMPONI in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). The relevant outcomes of the model are the total annual biologic costs, per member per month (PMPM), and per treated member per month (PTMPM) costs of treatment with subcutaneous biologics (i.e., SIMPONI, adalimumab, and etanercept). The model has the capability of estimating the financial impact, for 3 consecutive years, of other biologic agents used in the treatment of RA, PsA, or AS, including infliximab, abatacept, rituximab, However, only the FDA-approved subcutaneous biologics are used in the base case analysis. The budget impact can be reported for each of the three years separately (i.e. Year 1, Year 2, Year 3).

3.1.2 Model Structure

The model estimates the annual and per member budget impact of adding SIMPONI to the treatment options for patients with RA, PsA, and/or AS by comparing the costs expected with and without SIMPONI. The model can be used to review the budget impact for all 3 indications (RA, PsA and AS), each indication individually, or in any combination. The budgetary impact of SIMPONI is calculated for a specified payer during a one-year time frame in the base case analysis (i.e., Year 1 only).

The model simulates two paths for this patient population:

1. SIMPONI is available and used by a proportion of patients with RA, PsA and/or AS. A proportion of the eligible patients receive SIMPONI 50 mg every month instead of currently marketed subcutaneous biologic agents. This path is scenario 1 named "market forecast."
2. SIMPONI is not used by this patient population. All eligible patients would receive currently marketed subcutaneously administered biologic agents. This path is scenario 2 named "without SIMPONI."

3.1.3 Parameter Estimates

Although most parameters (e.g., prevalence of the disease, proportion of patients receive treatment, proportion of patients treated with a biologic agent, proportion of patients treated with SIMPONI) were set to a base case scenario, it is possible for users to modify all parameters in order to better reflect their population of interest and existing biologic utilization.

3.1.3.1 Input Values

The default drug utilization information (e.g., annual doses of each agent) was based on the labeled maintenance dosing for each agent, as presented in **Table 3-1**. Induction doses are not included in the model, as these costs are higher for all therapies and are time-limited. The true costs to the payer will result from maintenance dosing of medication.

For SIMPONI, dosing of 50 mg every month was used in the base case, for a total of 12 administrations per year (SIMPONI PI). Etanercept labeled dosing consists of 50 mg doses every week, for a total of 52 doses per year (Enbrel PI). Labeling for adalimumab in the base case consists of maintenance dosing of 40 mg every other week for a total of 26 injections per year (Humira PI).

3.1.3.2 Patient Population

The patient population for this model includes adults (age 18 and older) with RA, PsA and/or AS and who are eligible for treatment with biological therapy. The base case model used a hypothetical plan population of 1 million covered lives; however, users of the model

can enter the plan's own population data. The treated patient population for a particular payer could be defined by applying population-based incidence of RA, PsA and AS to the total number of payer covered lives.

3.1.3.3 Treatment Cost

Default data on WAC are provided for the users and are derived from Red Book pricing from August 2008 (2008 Red Book® UPDATE. Montvale, NJ: Thomson PDR; August, 2008). Annual per patient drug costs were derived by multiplying the WAC price by the number of annual administrations) (**Table 3-1).** The model assumes that the administrative costs for injections are the same for all agents, and not included in the model. For the base case model, it is assumed that the lowest prescribed dose of all biologic agents will be used in all patients, and that no double-dosing of comparator products will occur. However, users of the model may alter the percentage of patients who may require doses adjustment, or double doses of Enbrel, or Humira to demonstrate the impact of increased dosing on their budget.

Table 3-1. Wholesale Acquisition Cost and Annual Per Patient Cost

	Recommended dose	WAC treatment cost	Recommended Number of Doses per Year	Annual per patients cost
SIMPONI™ (golimumab)	50mg ***once monthly***	$1,575.00	12	$18.900.00
Humira®(adalimumab)	40mg ***every other week***	$726.40	26	$18.886.40
Enbrel® (etanercept)	50mg ***weekly***	$363.20	52	$18.886.40

3.1.3.4 Other Cost

This model assumes that there are no clinically significant differences in the rates of adverse events requiring treatment for the different treatment arms. Hence, the model does not make specific adjustments to costs and quality of life to account for adverse events. No clinical efficacy or adverse events included in this model.

Other outcomes and costs not included in the model include the costs associated with healthcare resource utilization, laboratory tests, patients with untreated RA, PsA and AS, and lost productivity and disability.

3.1.4 Perspective, Time Horizon and Discounting

The model perspective is that of a managed care organization (MCO) covering RA, PsA and/or AS patients.

The base case model describes a static, one year timeframe of maintenance treatment with subcutaneous therapy for patients with RA, PsA and/or AS. The base case model assumes there are no discounts or rebates to the plan for any of the treatment options; however users of the model can edit these fields to input any relevant discount or rebate received.

3.1.5 Analyses

The relevant outcomes of the model are the total annual biologic costs, per member per month (PMPM) cost, and per member per treated member of treatment with subcutaneous biologics.

The model defines a treatment mix for the following two groups:

1. A population of patients for which SIMPONI is available (Scenario 1: Market Forecast).
2. A population of patients for which SIMPONI is not available (Scenario 2 without SIMPONI).

In the base case scenario (i.e., model's default data), the treatment mix is set to match current market share data available for previously-approved subcutaneous biologic agents. The intravenously-administered agents [Orencia® (abatacept), Remicade® (infliximab), and Rituxan® (rituximab) are

not included in this analysis; therefore, the percentage of biologic-eligible patients assigned to each treatment group does not sum to 100%.

In the population where SIMPONI is available, SIMPONI is assumed to be used. Where used, it is assumed to replace a commensurate proportion of the baseline distribution of biologic agents. In both groups, the proportion of patients treated with any biologic agent is fully customizable to local payer needs.

3.1.6 Presentation of Results

Table 3.2 summarizes the patient populations who receive biologic treatment for each indication.

Table 3.2 Patient populations who receive biologic treatment

	RA	PsA	AS	All	Number of patients
Prevalence	0.6%	0.25%	0.13%	0.98%	9,800
Diagnosed	85%	55%	55%	73%	7,190
Eligible for biologics	20%	12%	13%	18%	1,278
Penetration	58.9%	74.1%	82.2%	63.5%	799

For the base case model, it was assumed that RA, PsA and AS affected approximately 0.98% of the plan's population, based on the proportion of the United States (US) population affected by RA. PsA and AS (Helmick CG, 2008, Gelfand JM, 2005, Cater et al., 1979). Of those, an estimated 73% were estimated to be diagnosed (Decision Resources, 2007 and 2008), and 18% of diagnosed patients received biologic treatment (SDI, 2008). Of those patients who received biologic therapy, 63% were taking SC biologics. Furthermore, it was assumed that SIMPONI had 3% share among all biologics. Thus, the market share of SIMPONI among SC biologics was 4.7% (3%/63.5%).

Table 3-3 Market shares of SC biologics with or without SIMPONI.

Market Share	RA	PsA	AS	Total
Without SIMPONI™				
Humira®	23.0%	26.8%	34.1%	24.7%
Enbrel®	35.8%	47.3%	48.1%	38.8%
Total	58.8%	74.1%	82.2%	63.5%
With SIMPONI™				
SIMPONI™	3.0%	3.0%	3.0%	3.0%
Humira®	21.5%	25.3%	32.6%	23.2%
Enbrel®	34.3%	45.8%	46.6%	37.3%
Total	58.8%	74.1%	82.2%	63.5%

Table 3-4 illustrates when adding SIMPONI to the mix of treatments for RA, PsA and AS. The model demonstrates that the addition of SIMPONI to the treatment mix has no impact on the total annual treatment cost, PMPM, as well as PTMPM.

	Scenario 1: with SIMPONI	Scenario 2 without SIMPONI	Difference (Scenario 1 - Scenario 2)	Proportional difference in cost
Total costs	$15,089,660	$15,089,146	$514.01	0.00%
PMPM	$1.26	$1.26	$0	0.00%
PTMPM	$1,573.92	$1,573.87	$0.05	0.00%

The model demonstrates that the addition of SIMPONI to the treatment mix has no impact on the total annual treatment cost as well as PMPM.

3.1.7 Sensitivity Analysis

The above budget impact analysis, which was based on the projected market share for the treatment, may be subject to uncertainty due to the environment changes. The base case budget impact model assumed a health plan with an adult population size of 1,000,000, with 0.98% prevalence rate of RA, PsA and AS. Of those, it was estimated that 73% were diagnosed (7,190 patients). Within those diagnosed patients, 11.1% (799 patients) were treated with SC biologics. In the base model, the market share of SIMPONI was assumed as 3.0%. However, due to the uncertainty of the market share, these rates may vary.

A one-way sensitivity analysis was performed to test how robust of budget impact model by varying the assumptions of market shares 3.0% in either direction. Because the projected shares of SIMPONI were low, the lower limit of the tested range was 0% (**Table 3-10**).

Table 3-10. Market Share Sensitivity Analysis

Product	%	Patients treated	Total Annual Impact	Cost per patient	Cost PMPM
SIMPONI™ (golimumab)					
Base case	3.0	799	$15,089,660	$1,573.92	$1.26
Lower limit	0.0	799	$15,089,146	$1,573.87	$1.26
Upper limit	6.0	799	$15,090,174	$1,573.97	$1.26

Under this sensitivity analysis, the maximum impact of SIMPONI uptake at 6.00% market share is $1,574 per patient per month. Due to parity WAC pricing among the three subcutaneous biologic agents, there is no impact on the budget, when adding SIMPONI to the formulary.

Due to its unique formulation, less frequent dosing, and high efficacy, SIMPONI offers a first-line alternative to the currently available subcutaneous biologic agents approved for the treatment of RA, PsA and AS, with minimal budgetary impact from a national and health plan perspective. Furthermore, it offers an opportunity for patients who have initially failed other subcutaneous biologic agents.

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4.0 PRODUCT VALUE AND OVERALL COST

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic, progressive disease that often appears between 30 and 50 years of age, and results in reduced quality of life, loss of function, work disability and increased mortality over time. According to the Arthritis Foundation, approximately 1.3 million Americans have RA. Consequently, this disease places a significant burden on the healthcare system and the society as a whole. Earlier, more aggressive treatment may significantly reduce or stop bone erosion and functional decline that can occur even in the early stages of the disease, thus reducing treatment costs.

Although MTX is generally considered the first-line DMARD in RA, a subset of patients will not respond adequately to MTX. Those that do respond are likely to see an attenuation of response over time. Thus, in RA there is an unmet medical need among patients who are unlikely to respond or are inadequately responding to MTX for an agent that effectively reduces the signs and symptoms of RA. SIMPONI has been studied in MTX-naïve and MTX refractory patients with active RA in multicenter, randomized, double-blind, placebo-controlled phase III studies.

Further, although anti-TNF agents (etanercept, adalimumab, and infliximab) are available for the treatment of RA, not all patients achieve a satisfactory treatment response with initial therapy. Thus, in RA there is an unmet need among patients who have previously been treated with anti-TNF agents for an agent that effectively reduces the signs and symptoms of RA. SIMPONI is the first anti-TNF agent to be studied in a multicenter, randomized, double-blind, placebo-controlled phase III study in patients previously exposed to anti-TNF therapy.

SIMPONI is the only anti-TNF biologic that is approved for once monthly subcutaneous dosing for the treatment of MTX naïve, MTX refractory, and active RA patients who have previously been treated with anti-TNF agents. SIMPONI, in combination with MTX, is effective in the treatment of moderately to severely active RA, as demonstrated in three phase III clinical trials (Emery et al, 2008; Keystone et al, 2008; Smolen et al, 2008). In these studies, treatment with SIMPONI plus MTX was significantly better than MTX alone in patients with moderately to severely active RA based on the following parameters:

- Improvement in the signs and symptoms of RA, as measured by ACR 20, 50, and 70 responses at weeks 14 and 24.
- Improvement in physical function response as measured by change in HAQ scores from baseline at week 24.
- Improvement in productivity scores and time lost from work at week 24.

PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) is a chronic, inflammatory, usually rheumatoid factor (RF)-negative arthritis associated with psoriasis. PsA usually involves multiple peripheral joints, the axial skeleton, sacroiliac joints, fingernails, and entheses. Affecting men and women equally, PsA peaks between the ages of 30 and 55 years. According to the National Psoriasis Foundation, an estimated 1 million adults in the United States suffer from PsA Over one-third of patients with PsA also develop dactylitis and enthesopathy.

Most of the treatments currently used have been adapted from experience in the RA patient population or in the treatment of psoriasis. Therefore, there are limited clinical study data to support the efficacy and/or safety in PsA for most of the agents used to treat active PsA The available data indicate that traditional DMARDs do not inhibit structural damage in PsA. Patients taking these medications may suffer dose limiting side effects, including gastrointestinal, hepatic and renal toxicities.

SIMPONI therapy satisfies an unmet need for a treatment that results in significant levels of improvement in the joint and skin components of active PsA. SIMPONI, with or without concomitant MTX, is effective in the treatment of patients with active PsA, who have had inadequate response to NSAIDS and/or DMARDS (Kavanaugh et al, 2009). In this study, treatment with SIMPONI was significantly better than placebo in patients with active PsA based on the following parameters:

- Improvement in the joint and skin symptoms of active PsA, as measured by ACR 20, 50, and 70 responses at weeks 14 and 24, as well as PASI 75 and 90 responses at week 24.
- Improvement in physical function response, as measured by change in HAQ scores from baseline at week 24.
- Improvement in productivity scores and time lost from work at week 24.

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic, progressive, painful inflammatory rheumatic disease, which affects the axial skeleton, primarily the sacroiliac joints. AS typically affects young people, beginning between the ages of 15 and 30, and can result in gradually progressive stiffness and limited spinal mobility and chest expansion. Additionally, AS results in considerable burden to the patient leading to decreased quality of life (QoL), work disability, and increased mortality.

Currently, the mainstay of treatment for patients with AS is limited to NSAIDs and physical therapy. Few studies have been done with DMARDs and DMARDs have not been proven to be clearly effective for axial disease.

Anti-TNF therapy has been shown to be effective in patients with AS, particularly those patients who are unresponsive to conventional therapy. SIMPONI therapy satisfies an unmet need for a treatment that results in significant levels of improvement in the symptoms of active AS. SIMPONI as monotherapy is effective in the treatment of patients with active AS, who have had an inadequate response to current or previous NSAIDs and/or DMARDs (Inman et al, 2008). In the GO-RAISE study, treatment with SIMPONI was significantly better than placebo in patients with active AS based on the following parameters:

- Improvement in the signs and symptoms of active AS, as measured by ASAS 20 and 40 responses at weeks 14 and 24.
- Improvement in physical function response as measured by change in BASFI scores from baseline to week 24.
- Improvement in productivity scores at week 24.

SIMPONI PROVIDES ECONOMIC VALUE

As noted in the modeling report for SIMPONI, the WAC price is $1575.00. Therefore, a budget impact model (BIM) illustrated that the addition of SIMPONI to the treatment mix for RA, PsA and AS will have no impact on the total annual treatment cost for RA, PsA or AS, PMPM, as well as PTMPM.

5.0 SUPPORTING INFORMATION

5.1 REFERENCES

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5.2 ENCLOSURES

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APPENDICES

Appendix A: American College of Rheumatology (ACR) Criteria

ACR responses are usually presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response (Felson et al, 1995) is defined as a ≥ 20% improvement in:

1. Swollen joint count (66 joints) and tender joint count (68 joints)
   -AND-
2. ≥ 20% improvement in 3 of the following 5 assessments
   a. Patient's assessment of pain (VAS)
   b. Patient's global assessment of disease activity (VAS)
   c. Evaluator's global assessment of disease activity (VAS)
   d. Patient's assessment of physical function as measured by the HAQ
   e. CRP

ACR 50 and ACR 70 are similarly defined.

Appendix B: Disability Index of the Health Assessment Questionnaire (HAQ)

The functional status of the subject will be assessed by means of the Disability Index of the HAQ (Fries et al, 1980). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area are scored from 0, indicating no difficulty, to 3, indicating inability to perform a task in that area.

Appendix C: Disease Activity Score in 28 Joints (DAS28)

DAS28 is statistically derived index combining tender joints (28 joints), swollen joints (28 joints), ESR, and patient global VAS (van der Cruyssen, 2005). The DAS28 is a continuous parameter and is defined as follows:

DAS28 = 0.56 x SQRT (28TJC) + 0.28 x SQRT (28SJC) + 0.70 x In (ESR) + 0.014 x pt Global VAS where:

1. 28TJC is 28 joint count for tenderness
2. 28SJC is 28 joint count for swelling. The set of 28 joint count is based on evaluation of the shoulder, elbow, wrist, metacarpalphalangeal (MCP) 1, MCP2, MCP3, MCP4, MCP5, proximal interphalangeal (PIP) 1, PIP2, PIP3, PIP4, PIP5 joints of both the upper right extremity and the upper left extremity, as well as the knee joints of the lower right and lower left extremities.
3. ESR is the erythrocyte sedimentation rate.
4. SQRT (28TJC) is the square root of 28TJC.
5. SQRT (28SJC) is square root of 28SJC.
6. Patient global VAS is patient's global assessment of disease activity on a visual analogue scale of 100 mm.

DAS28 response criteria are defined in the table below (van Riel et al, 2000).

DAS28 Response Criteria			
	Improvement from Baseline		
DAS28 at visit	>1.2	>0.6-1.2	≤ 0.6
≤ 3.2	Good response	Moderate response	No response
>3.2-5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Subjects are considered to have a DAS28 response if they have a good or moderate response.

Appendix D: European League Against Rheumatism (EULAR) Criteria

The EULAR criteria is a DAS-based assessment tool used to measure individual response and classifies patients as non-responders, moderate responders or good responders based on the level of disease activity and its change from baseline (van Gestel, 1996 and van Gestel, 1998).

A change of 1.2 in a patient's DAS is considered a significant change. DAS is divided into 3 categories according to disease activity:

1. Low
2. Moderate
3. High

The EULAR response criteria using DAS and DAS28 is provided in the table below.

DAS at endpoint	DAS28 at endpoint	Improvement in DAS or DAS28 from Baseline		
		≤ 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 2.4	≤ 3.2	Good		
>2.4 and ≤ 3.7	>3.2 and ≤ 5.1		Moderate	
>3.7	>5.1			None

Appendix E: Functional Assessment of Chronic Illness Therapy (FACIT-F)

The FACIT-F is a questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue (Cella et al, 2002; Yellen et al, 1997). The total FACIT-F score ranges from 0 to 52 with a higher score indicating less fatigue. It has been used in clinical studies of subjects with RA and has demonstrated sensitivity to change in these subjects (Chartash et al, 2003).

Appendix F: Psoriatic Arthritis Response Criteria (PsARC)

The PsARC is an assessment tool specifically designed for patients with psoriatic arthritis (Clegg et al, 1996). There are 4 measures in the PsARC and they include:

1. Patient self-assessment (0-4)
2. Physician assessment (0-4)
3. Joint pain/tenderness score
4. Joint swelling score

A clinical improvement is defined as a decrease by 1 from the Patient self-assessment or the Physician assessment or a decrease by 30% in the Joint pain/swelling score or the Joint swelling score.

A treatment response is defined as an improvement in at least 2 out of 4 measures and must include joint pain/tenderness or welling score and no worsening in any of the 4 measures.

Appendix G: Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy (Fredricksson and Pettersson, 1978). The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and scaling, which are each rated on a scale of 0 to 4.

The scoring system for the signs of the disease (erythema, induration, and scaling) is: 0=none, 1=slight, 2=moderate, 3=severe, and 4=very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.

0=no involvement
1=1% to 9% involvement
2=10% to 29% involvement
3=30% to 49% involvement
4=50% to 69% involvement
5=70% to 89% involvement
6=90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

a. The neck is considered part of the head
b. The axillae and groin are part of the trunk
c. The buttocks are part of the lower extremities

The PASI formula* is:
PASI=0.1(Eh + 1h + Sh) Ah + 0.3 (Et + It + St) At + 0.2 (Eu + Iu + Su) Au + 0.4 (El + Il + Sl) A1

*Where E = erythema, I = induration, S = scaling, and A = area

Appendix H: Nail Physician's Global Assessment (Nail PGA)

The Nail PGA is used to determine the status of a subject's nail psoriasis at a given time point. Nails are graded on a scale of 1 to 5 (1-none, 5-very severe).

Appendix I: Nail Psoriasis Severity Index (NAPSI)

The NAPSI is a numeric tool for evaluation of nail psoriasis (Rich and Scher, 2003). The scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis by area of involvement in the nail unit. A target nail representing the worst nail psoriasis is divided into quadrants and is graded for nail matrix psoriasis and nail bed psoriasis. The sum of these 2 scores is the total NAPSI score.

Nail matrix psoriasis consists of any of the following: pitting, leukonychia, red spots in the lunula, and nail plate crumbling.

Score for matrix psoriasis

0 = none
1 = present in 1/4 nail
2 = present in 2/4 nail
3 = present in 3/4 nail
4 = present in 4/4 nail

Nail bed psoriasis is the presence of any of the following: onycholysis, splinter hemorrhages, oil drop discoloration, and nail bed hyperkeratosis.

Score for nail bed psoriasis

0 = none
1 = present in 1/4 nail
2 = present in 2/4 nail
3 = present in 3/4 nail
4 = present in 4/4 nail

Appendix J: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI measures the level of disease activity in patients with AS and consists of 10 cm visual analog scales used to answer 6 questions pertaining to 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain/swelling
4. Areas of localized tenderness
5. Morning stiffness

The questions are scored on a severity scale from 0 (none) to 10 (very severe). The following 6 questions make up the BASDAI questionnaire.

1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of AS neck, back or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of discomfort you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up?

To give each symptom equal weighting, the mean of the two scores from questions 5 and 6 relating to morning stiffness is taken and added to the totals from question 1 to 4. The resulting 0 to 50 score is divided by 5 to give a final 0-10 BASDAI score (Garrett et al, 1994).

Appendix K: Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of ten questions designed to determine the degree of functional limitation in those with AS (Calin et al, 1994). The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the patients' ability to cope with everyday life.

The questionnaire is made up of the following ten questions below.

1. Putting on your socks or tights without help or aids (e.g. sock aid)?
2. Bending forward from the waist to pick up a pen from the floor without an aid?
3. Reaching up to a high shelf without help or aids (e.g. Helping Hand)?
4. Getting out of an armless dining chair without using your hands or any help?
5. Getting up off the floor without help from lying on your back?
6. Standing unsupported for ten minutes without discomfort?
7. Climbing 12-15 steps without using a handrail or walking aid (one foot on each step)?
8. Looking over your shoulder without turning your body?
9. Doing physically demanding activities (e.g. physio exercises, gardening, sport)?
10. Doing a full day's activities at home or at work?

A 10 cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score - a value between 0 and 10.

Appendix L: Bath Ankylosing Spondylitis Metrology Index (BASMI)

The BASMI scale is used to determine the minimum number of clinically appropriate measurements that assess accurately axial status and to define clinically significant changes in spinal movement (Jenkinson et al, 1994).

Axial status is regarded as cervical, dorsal, and lumbar spine, hips and pelvic soft tissue. The following 5 clinical measurements are included in the index:

1. Cervical rotation
2. Tragus to wall distance
3. Lumbar side flexion
4. Modified Schober's
5. Intermalleolar distance

The scale for evaluating a BASMI score is provided in the table below.

Clinical Measures	**Score**		
	0	**1**	**2**
Tragus to wall	<15 cm	15-30 cm	>30 cm
Lumbar flexion	>4 cm	2-4 cm	<2 cm
Cervical rotation	>70°	20-70°	<20°
Lumbar side flexion	>10 cm	5-10 cm	<5 cm
Intermalleolar distance	>100 cm	70-100 cm	<70 cm

BASMI 0 = mild disease involvement, 1 = moderate disease involvement, and 2 = severe disease involvement. The mean of the ten scales gives the BASMI score - a value between 0 and 10.

Appendix M: 36-Item Short Form Health Survey (SF-36)

The SF-36 is a measure of health status made up of 36 questions. The questions are grouped into 8 scales (Pollard et al, 2005).

1. Physical functioning (PF)
2. Role-physical (RP)
3. Bodily pain (BP)
4. General health (GH)
5. Vitality (VT)
6. Social functioning (SF)
7. Role-emotional (RE)
8. Mental health (MH)

There are two summary measures that aggregate the 8 scales:

1. Physical Health (PF, RP, BP, GH)
2. Mental Health (VT, SF, RE, MH)

All but one of the 36 items is used to score the 8 SF-36 scales and each item is used in scoring only one scale.

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